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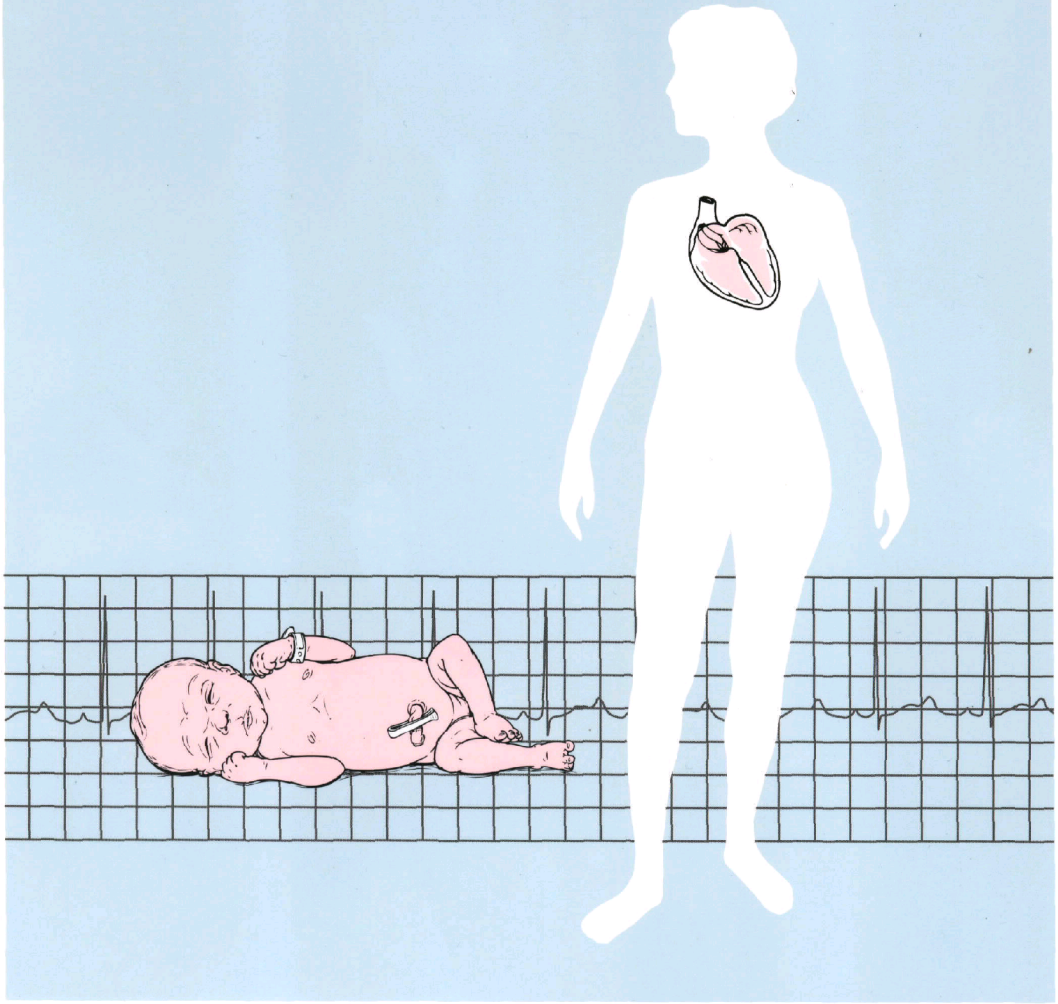
NEONATAL INTENSIVE CARE



NEONATAL INTENSIVE CARE

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This book is part of the SpaceLabs Medical Clinical Information & Technology Book Series for biomedical and clinical professionals. The series is an educational service of SpaceLabs Medical, a leading provider of patient monitoring and clinical information systems.

Published by SpaceLabs Medical, Inc.,
Redmond, Washington, U.S.A.

Printed in the United States.

ISBN 1-882588-50-9

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INTRODUCTION

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Neonatology and technology have been partners throughout the modern era of neonatal acute care. Clinical trials of a controlled thermal environment, beginning in 1958, provided an outstanding example of achievements made possible by the collaboration of basic research, industry, and technology. These studies clearly demonstrate a favorable influence of temperature control devices on patient outcome. A massive volume of research during the next two decades fostered development of increasingly sophisticated bedside care techniques in the neonatal intensive care unit (NICU). These were supported by a growing array of devices for ventilatory support, oxygen monitoring, parenteral infusions, and measurement of numerous physiological parameters. Many of these functions could be carried out on a continuous basis. More recently, computers have appeared in the NICU, accompanied by a growing volume of new software to assist care providers in storing, analyzing, and displaying monitored data.

Such advances have not been without a downside, however. Neonatal intensive care has become increasingly intrusive and invasive. It is the most expensive medical care in the world and technology is a major driving force for the cost. Yet, use of increasingly complex medical devices has opened new avenues for patients, providers, and manufacturers alike.

Several things seem clear regarding the future of neonatal monitoring technology in this healthcare environment with its emphasis on cost containment. First, purchase of new equipment will require increasingly stringent justification as to clinical efficacy and impact on outcome. Second, manufacturers will be held to much higher standards of proof regarding performance of the equipment being marketed. Finally, physicians and other care providers will bear a heavy responsibility to thoroughly understand the technical aspects and pitfalls of sophisticated monitoring devices.

1.0 NEONATAL ELECTROCARDIOGRAPHY

A significant proportion of all pediatric cardiac arrhythmias have their presentation in the neonatal period. Therefore, it is imperative that those who care for newborns (and fetal patients) be aware of the modes of presentation and diagnostic electrocardiographic features of neonatal arrhythmias. There are distinct differences in the diagnosis and management of these arrhythmias, even compared to that of later childhood. The purpose of this section is to describe some of the more common elements of neonatal arrhythmia presentation, from the fetus to the 6-month-old infant.

1.1 Fetal Arrhythmias

With the advent of more frequent ultrasonographic scanning of the fetus, cardiac rhythm abnormalities are being detected with equally greater frequency. Determination of cardiac mechanical events by means of fetal echocardiography remains the only practical means of determining fetal cardiac electrical activity. Wall motion and Doppler interrogation of valve flows pertaining to either the atria or ventricles imply a preceding cardiac electrical event. Therefore, the relationship of these events can be used to derive a "fetal ECG analog" consisting of specifically timed atrial and ventricular events.

Diagnoses begin by a simple determination of rate. The ranges for normal gestational age-appropriate heart rates have not been established, but the general consensus is that a fetal rate in excess of 200 beats per minute (bpm) at any time during gestation constitutes tachycardia. Suspicion is also warranted for cardiac rhythms that are incessant at 160 bpm to 200 bpm, because some forms of supraventricular tachycardia (SVT) may present in this fashion. Rhythms that are too slow are those that are consistently under 100 bpm to 110 bpm. Irregular rhythms are common and often are found to be secondary to premature atrial contractions (PACs).

An analysis of the implied cardiac rhythm can be made by establishing the relationships of atrial and ventricular wall motions and/or Doppler signals from atrioventricular valves or semilunar valves. A discussion of each rhythm is beyond the scope of this section, but the implication that a fetal tachyarrhythmia is ventricular tachycardia rather than a form of SVT has bearing on therapeutic intervention.

Transplacental therapy (giving antiarrhythmic agents to the mother) is possible and indicated for tachyarrhythmia therapy, as fetal nonimmune hydrops can change rapidly and with adverse effect if tachycardia is left untreated. Some agents used with relative frequency include digoxin, procainamide, propranolol, flecainide, mexiletine, and amiodarone, depending on the rhythm abnormality, the gestational age, and the relative urgency of therapy. The overall goal is to bring about delivery of the infant at a gestational age carrying low risk of immature pulmonary development and respiratory distress.

1.2 Electrocardiography

The recording speed for most electrocardiograms is 25 millimeters per second (mm/sec). Consequently, the 1 mm distance between each fine line on the ECG recording paper is 0.04 sec (40 msec) and the 5 mm distance between the heavier lines is 0.20 sec

(200 msec); isolated lines at the top of the paper represent a period of 3.0 sec. The heart rate can be calculated by either dividing 60,000 by the R-to-R interval in milliseconds, or it may be estimated by the observation that R waves separated by one large box indicate a rate of 300 bpm, by two large boxes, 150 bpm, by three large boxes, 100 bpm, and by four large boxes 75 bpm.

The newborn QRS complex is narrower than the adult QRS. The mean QRS duration in a newborn is 50 msec, whereas the adult mean is > 70 msec. R wave detection systems need to account for this normal, age-related variation in cardiac signals. Additionally, narrow QRS complexes can be interpreted as pacemaker spikes, if there is a pacing spike detection feature in the monitor. Double-counting may result, falsely leading to high heart rate alarms. Of more concern is the overdetection of pacemaker spikes as QRS complexes. Loss of ventricular capture may not be detected by a monitor if the pacing spike is interpreted as a QRS complex. A narrow margin of safety between pacing spike and QRS complex detection is therefore unacceptable in the newborn patient.

The electronic amplifier is designed for an increased QRS detection range relative to the minimum QRS amplitude. Detection of lower amplitude signals improves the ability to measure heart rates in neonatal and pediatric patients. This difference is supported by the *AAMI Standard for Cardiac Monitors, Heart Rate Meters, and Alarms.*

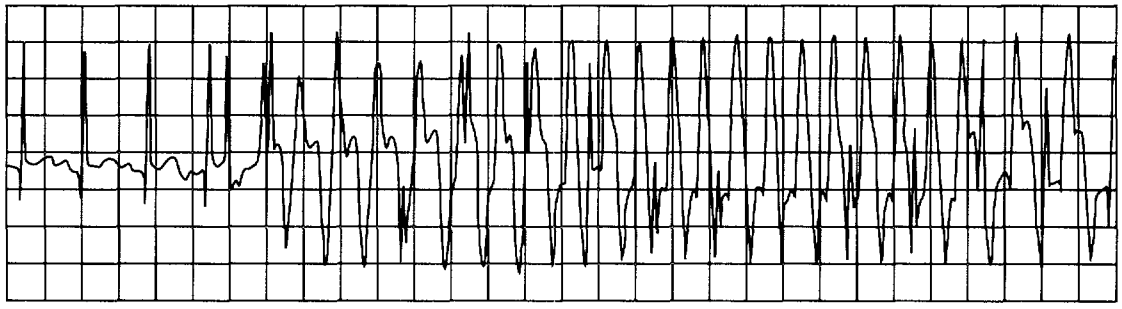
Artifactual recordings in pediatric electrocardiography are a frequent cause of concern and alarm. Artifact can be due to faulty monitoring technique, patient noncompliance and patient activities that give the appearance, particularly on bedside monitors, telemetry units, and ambulatory monitors, of both regular and irregular cardiac rhythm abnormalities.

Faulty monitoring techniques can be avoided by correct skin preparation prior to placing ECG electrodes. In infants and small children, it is best not to attach limb electrodes on the limbs themselves. With small patients, arms and legs tend to move without warning and cause wandering baselines and other low-frequency motion artifacts. Electrodes are best placed on the torso, on the shoulders, and lower abdominal quadrants where motion is more limited. The skin must be clean, and electrodes should not be placed over skin creases. Adequate contact and adhesion of each electrode must be ascertained, without buckling of the electrode patch. Use of electrode gels and suction bulbs is almost nonexistent these days, but precordial smear patterns can be produced when gel allows continuous contact between electrodes. For Holter monitors, tincture of Benzoin improves stability of the electrodes. Providing an extra stress loop and bundling lead wires prevents traction-induced electrode removal and limbs getting wrapped around lead wires. A loose electrode often results in high-frequency interference patterns. For ECGs, the key to obtaining a quality trace is patience. Distracting the infant for 10 to 15 seconds is enough to obtain most computer-generated, simultaneous lead ECGs.

Artifact tracings are often due to patient activities (Figure 1.1). They include chest physiotherapy, tapping on the electrode, high-frequency jet ventilators, burping, jostling of small infants, and hiccups. These artifact patterns can be diagnosed as such by keeping in mind the following: the true P waves and QRS complex can often be found walking through the artifact, many artifacts result in R-to-R or P-to-P intervals which are nonphysiologic (> 400 bpm), there are no pauses at the end of the rapid rhythms, as one might expect, and the patient is asymptomatic.

Figure 1.1 — (a) Rapid sudden changes are due to chest physiotherapy. Narrow QRS complexes can be seen "walking through" the artifact; (b) Sharp rapid deflections due to a loose pin electrode.

(a)



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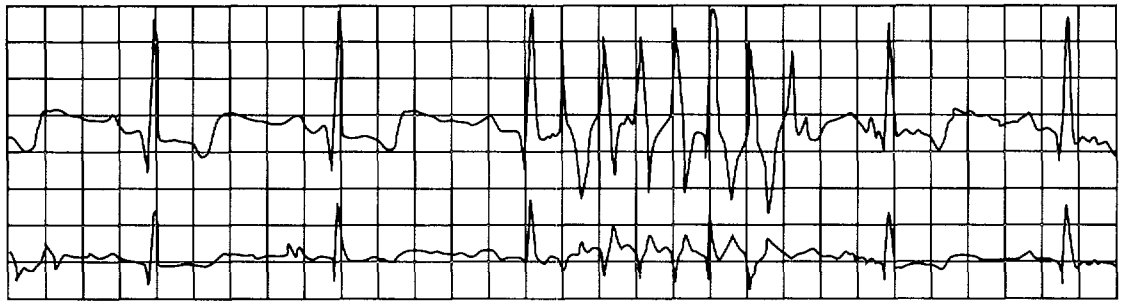


1.3 Bradycardias in Newborns

Bradycardia in the newborn nursery is a fairly common finding. Significant bradycardia can be defined as less than 70 bpm in the infant. The most frequent cause of slow ventricular rates is repetitive blocked PACs. The rhythm is often irregularly irregular, without a set pattern of regular rate and interspersed pauses. A careful inspection of the T waves prior to the pause will reveal high-frequency P waves (Figure 1.2). However, it is often necessary to obtain a full 15-lead electrocardiogram (standard 12 leads, plus V_3R, V_4R, and V_7) to see the blocked P waves adequately. Blocked PACs resolve without therapy and should not cause concern. Bradycardia may also result from apnea. The slow cardiac rate in this setting must be recognized as a secondary event.

Figure 1.2 — Frequent nonconducted PACs in a newborn resulting in an overall slowing of the ventricular rate.

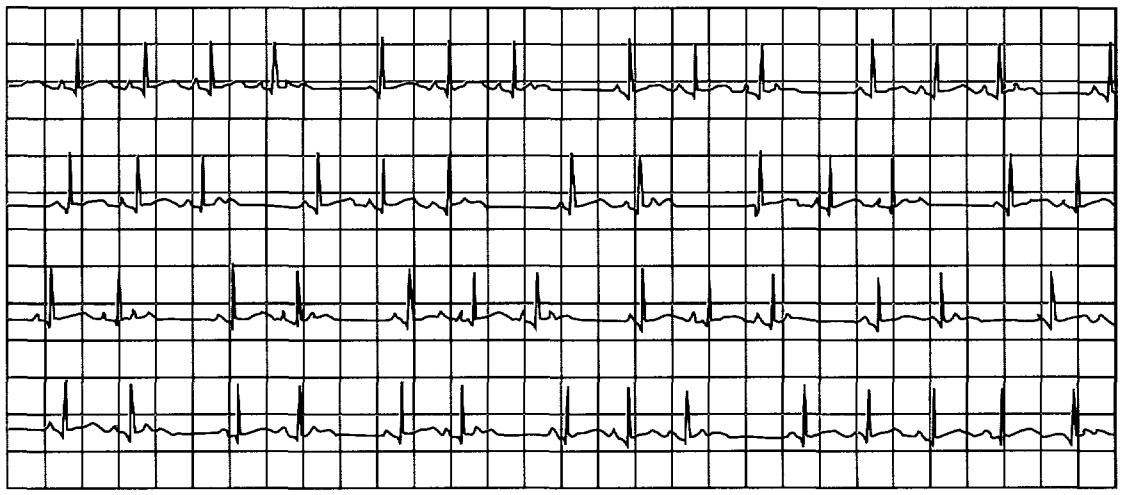
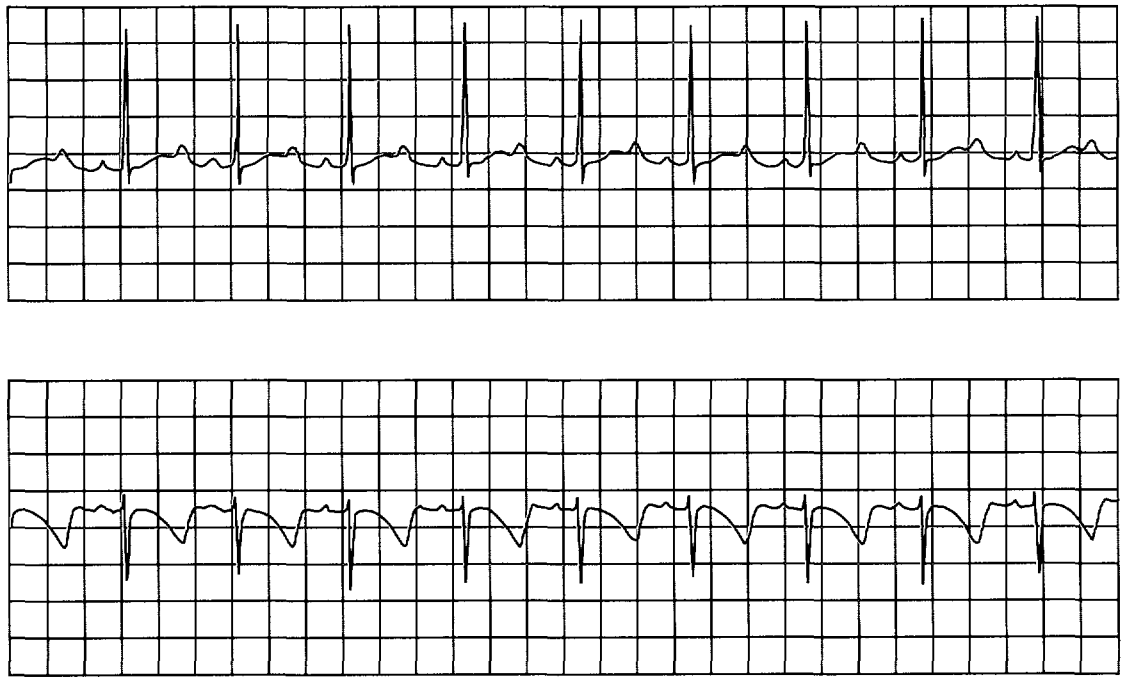


Figure 1.3 — Long QT syndrome and bradycardia in a young patient. The corrected QT (QTc) is prolonged (0.56 sec).

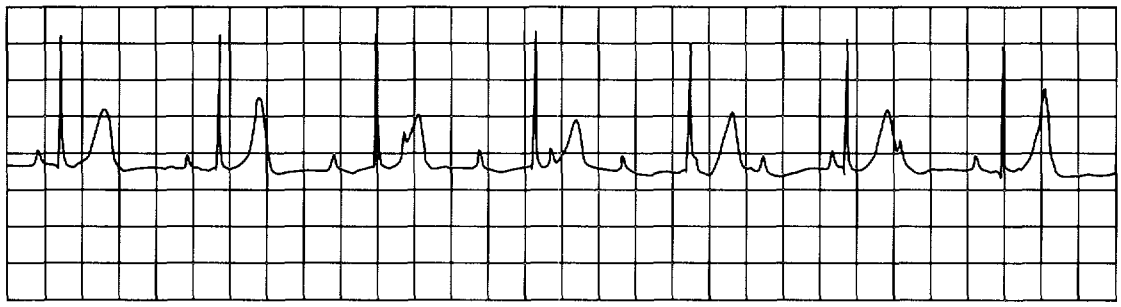


The most serious diagnoses to consider when newborn bradycardia is seen are those of the long QT syndrome (Figure 1.3) and congenital complete atrioventricular (AV) block (Figure 1.4). The association of long QT syndrome and sinus bradycardia has been recognized for several years. Measurement of the rate-corrected QT interval (QTc) using Bazett's formula is unfortunately far from routine. It is crucial to make this calculation of the QTc, where

$$QTc = \frac{QT}{\sqrt{R\text{-}R}}$$

as the syndrome may be familial and can dispose to torsade de pointes, ventricular tachycardia and sudden death. The upper value of a normal QTc using Bazett's formula is 0.44 sec.

Figure 1.4 — Congenital complete AV block.



Congenital complete AV block can present with slow junctional or ventricular rhythms. In the former, the QRS complex is the same morphology as that seen during sinus rhythm. The heart is often normal, but there may be evidence of maternal autoantibodies (anti-Rho) responsible for the developmental conduction system damage. Mothers may have evidence of lupus erythematosis. Abnormal hearts may also have complete AV block: 1-transposition of the great arteries, some single ventricle physiology states, tricuspid atresia and coarctation. The QT interval may be prolonged in up to 20% (in those with narrow QRS complexes) with an increased risk of sudden death.

1.4 Tachyarrhythmias in Newborns

As discussed previously, some newborn tachyarrhythmias can be diagnosed *in utero*. Some of these patients may actually stop having tachycardia after delivery. Many newborn superventricular tachycardias (SVTs) appear in the first several days of life. Given the current practice of sending newborns home at 24 hours, most have their first episode outside the hospital setting. As with bradycardia, a significant number occur between 1 and 8 weeks of age. The infants may present with a history of lethargy, pallor or mottling, poor feeding, diaphoresis, and/or vomiting. Many have actually been in tachycardia for several hours before the abnormality is detected. Other patients have SVT for a day or more and present in congestive heart failure.

The diagnosis is relatively easy to make once the ECG is performed. It is crucial to obtain a full 15-lead pediatric ECG due to the rightward orientation of the heart in the chest of infants. Usually, the presence of P waves, with a 1:1 relationship to QRS complexes, can be discerned and the diagnosis of SVT made (Figure 1.5). Primary atrial tachycardias and atrial flutter often have some degree of AV block and the P waves outnumber the QRS complexes, frequently in a 2:1 ratio (Figure 1.6).

When the diagnosis is difficult to make, use of a transesophageal recording and pacing catheter may be helpful. The esophagus sits directly behind the left atrium; atrial electrical activity can be recorded from a catheter inserted through the nose or mouth and placed in the esophagus near the atrium (Figure 1.7). The electrodes from the right arm and left arm are connected to the recording catheter and a bipolar transesophageal atrial electrogram is then recorded. The relationship to the QRS complex is then determined and the mechanism of the tachyarrhythmia revealed.

Acute therapy of narrow QRS complex tachycardias depends on the mechanism — the overwhelming majority are SVTs. Therefore, the initial treatment can consist of attempts at conversion using the diving reflex. A cold washcloth or, preferably, a surgical glove filled with ice and a little water, is abruptly placed over the infant's face for approximately 15 seconds. This initiates a vagal reflex that can terminate SVTs in the AV node region. If that fails, the next step generally includes use of intravenous adenosine, an agent that acts on potassium channels and calcium channels to block propagation of impulses through the AV node for a few seconds. If a transesophageal catheter is available, or has been used for diagnostic purposes, it can be used for overdrive pacing conversion of many SVTs. It is very important, whatever the method for terminating tachycardias, to record the event with a continuous 12-lead ECG, not just a rhythm strip from the bedside monitor. A great deal of information can be obtained at the time of conversion which can assist in subsequent management decisions. Occasionally, SVTs recur soon after termination and require more long-lasting therapy.

Intravenous use of digoxin and procainamide are useful in this regard. Intravenous propranolol and verapamil are contraindicated for use in infants and children under a year of age or so, due to the profound hypotension which can occur and the dramatic decrease in ventricular contractility in young patients given these drugs. Infants in particular have very catecholamine-dependent myocardial function. The use of an abrupt intravenous dose of beta-adrenergic blockade with a relative long half-life can be devastating. The infant presenting in shock may not have the time for transesophageal recordings or loading with intravenous medications. In those cases, direct current cardioversion using 0.5 joules/kg to 1.0 joules/kg is effective and appropriate.

Chronic treatment must take into account the natural history of many forms of SVT. Of all infants with SVT as newborns, 93% will be free of SVT by 8 months of age. This means that invasive forms of therapy, such as transcatheter radiofrequency ablation of arrhythmias, is unlikely to be necessary for the vast majority of patients in the first year of life. A third of those who have their SVT disappear, however, will experience a recurrence at a mean age of 8 years. Treatment for the infant with SVT must obviously be tailored to response, but aggressive medical management schemes are inappropriate in the first year of life, as many SVTs will abate spontaneously (Figure 1.8).

Figure 1.5 — Supraventricular tachycardia.

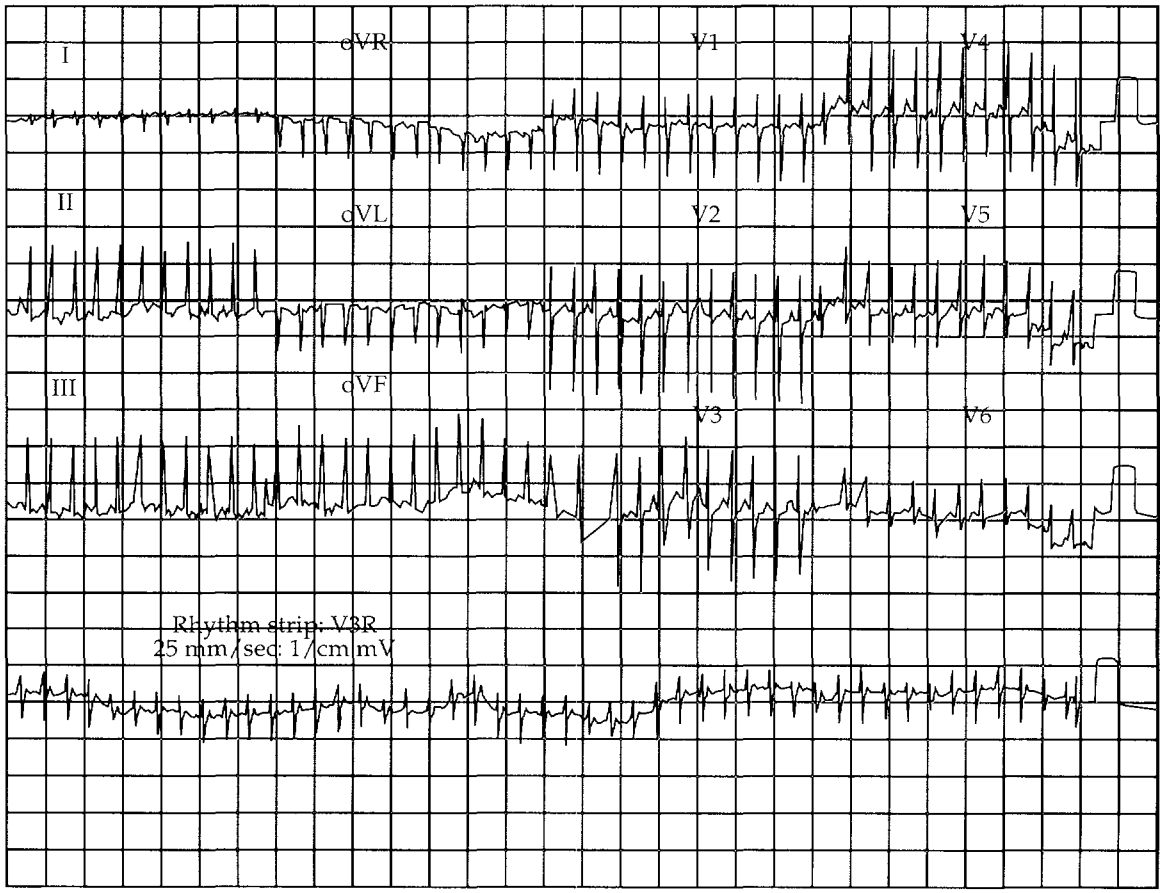
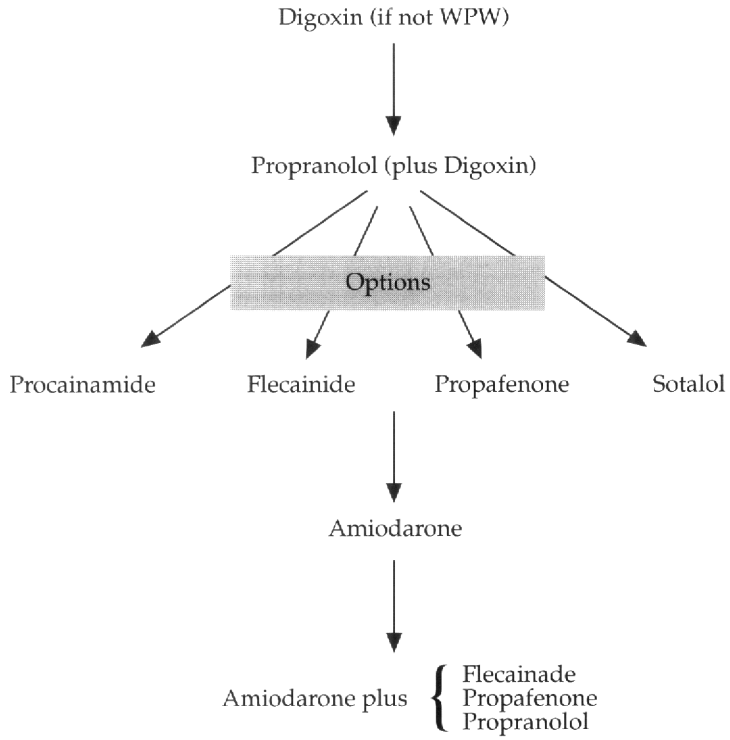


Figure 1.6 — Atrial flutter with a variable ventricular conduction.

Figure 1.7 — Atrial activity with a transesophageal atrial electrogram. This is atrial flutter with 2:1 AV conduction.

Figure 1.8 — Pharmacologic treatment for infants with chronic supraventricular tachycardia.



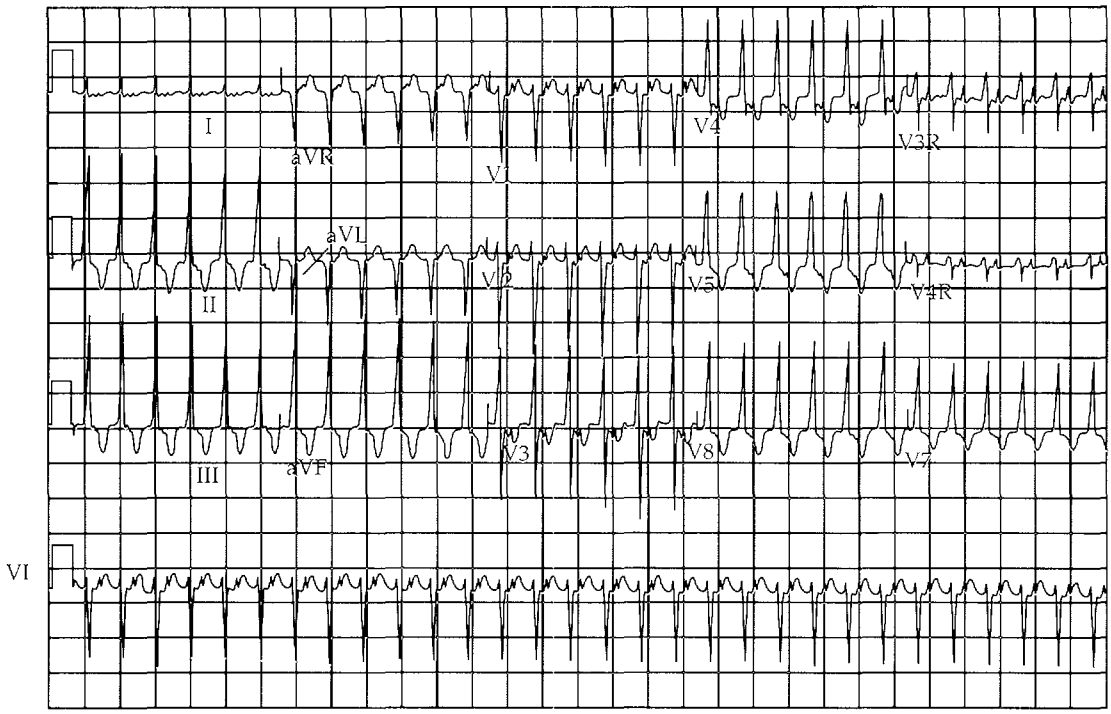
1.4.1 Wide QRS Complex Tachycardias in the Newborn

The diagnosis of a wide QRS complex tachycardia in a child or adult often implies a QRS duration in excess of 100 msec. However, in infants and small children, 80 msec to 90 msec, especially if the QRS morphology differs from that of sinus rhythm (Figure 1.9). Wide QRS complex tachycardias tend to present in similar fashion to most narrow QRS complex tachycardias. However, congenital junctional tachycardia and approximately one-third of infant ventricular tachycardias present with life-threatening shock.

Wide QRS complex tachycardias are rare in newborns and young children. Most represent a phenomenon of bundle branch block (particularly left bundle branch block in infants) during SVTs (Figure 1.10) and are, for the most part, hemodynamically stable rhythms. When tachycardias occur, one of the bundle branches often does not have an adequate time to recover before the next beat comes down the AV node and His bundle. There are complex electrophysiologic explanations for this phenomenon that are beyond the scope of this section. A 1:1 atrial-ventricular relationship during the wide QRS complex tachycardia (may require a transesophageal electrode) indicates a diagnosis of aberrant conduction during SVT, rather than ventricular

Figure 1.9 — (a) Wide QRS complex tachycardia in a newborn; (b) In sinus rhythm with an obvious difference in QRS morphology.

(a)



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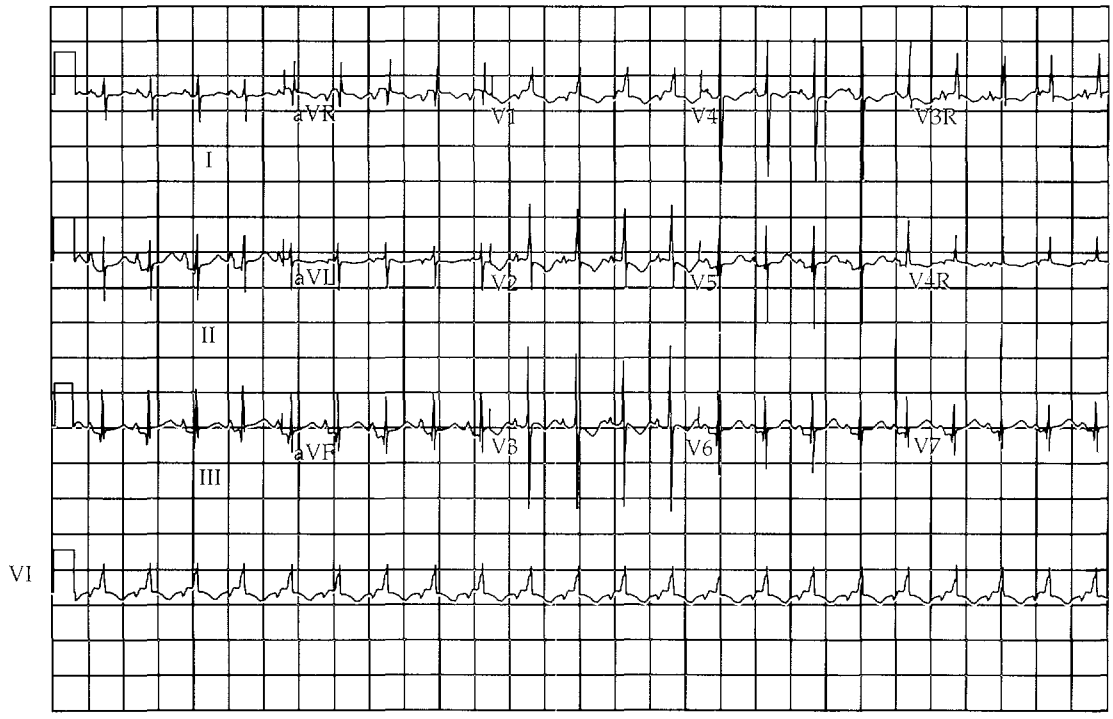
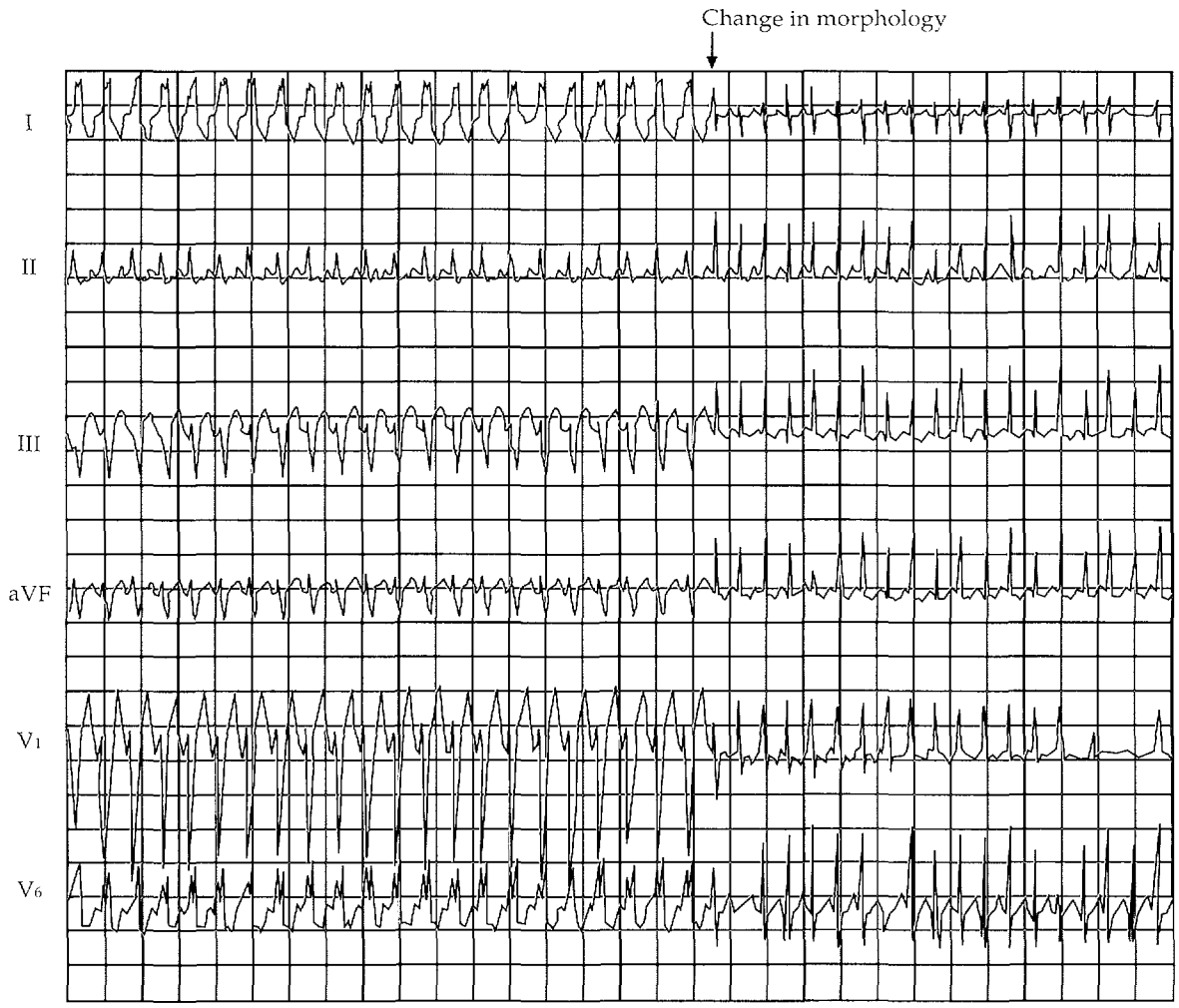


Figure 1.10 — Left bundle branch block pattern is seen on the left side of this illustration. The rhythm spontaneously changes to a normal QRS morphology at a slightly faster rate.



tachycardia. Occasionally, junctional tachycardias and ventricular tachycardias originating from the ventricular septum may have 1:1 retrograde conduction in newborns, making diagnosis difficult. Again, a 15-lead ECG is crucial to make the proper diagnosis. In this setting, the help of a pediatric cardiologist is necessary, especially if there is a suspected AV dissociation and the diagnosis of aberrant SVT is less likely.

If aberrant SVT is believed present, then acute therapy consists of intravenous adenosine. Therapy aimed at ventricular tachycardia consists of intravenous lidocaine and/or procainamide. Investigational intravenous amiodarone may prove helpful. Oral therapy (if the situation allows several days for drug steady-state to be reached) with beta-blockers, Class IC drugs, or amiodarone may be appropriate, depending on the specific diagnosis and hemodynamic state. Obviously, if the child is very ill, direct current cardioversion using 1.0 joule/kg to 2.0 joules/kg is appropriate.

1.5 Irregular Rhythms

By far the most common cause of irregular cardiac rhythms in infancy are PACs. This rhythm does not indicate any underlying cardiac abnormality and does not imply subsequent episodes of tachyarrhythmia. Actually, the infant with frequent PACs has likely been exposed to so many initiating events (the PACs themselves) for SVTs that if SVT has not occurred already, it is unlikely to do so. Often, the PACs are so frequent and early in the cardiac cycle that they are not conducted to the ventricules and, therefore, result in pauses. They may be conducted with aberrancy (Figure 1.11). Blocked atrial bigeminy can result in a slowing of the overall ventricular rate (Figure 1.12). This tends to be a transient phenomenon and, in the absence of other ECG abnormalities, does not warrant concern or therapy. The most important diagnosis to rule out in this setting is coexistent long QT syndrome, as mentioned previously. In the case of long QT syndrome, the PACs are not PACs at all, but regularly timed P waves that are not conducted (2:1 AV block) due to abnormal repolarization of the ventricles (Figure 1.13). Premature atrial contractions generally reset the normal sinus node mechanism. The finding of a less than compensatory pause after a premature beat often indicates a PAC has occurred. The compensatory pause is measured as twice the preceding P-to-P interval, beginning at the last sinus P wave.

Premature ventricular contractions (PVCs) are not as common as PACs in infancy. It is important to be sure that the PVCs are exactly that and not intermittent preexcitation of Wolff-Parkinson-White syndrome. A fully compensatory pause occurs most often, as the sinus node is not reset. However, this rule is often violated in infants due to the ease of retrograde conduction of the PVC activation through the AV node.

Rapid atrial tachycardias usually manifest variable degrees of AV block and result in irregular rhythms. The most common cause is newborn atrial flutter. While this arrhythmia requires intervention, it tends to be transient. Intravenous adenosine will block AV node conduction long enough to reveal the flutter waves, but rarely terminates flutter. Intravenous digoxin, procainamide, or transesophageal pacing are therapeutic options. Electrical cardioversion is rarely necessary.

Figure 1.11 — Conducted PAC (A), a blocked PAC (B), and a PAC (C) conducted aberrantly to the ventricles.

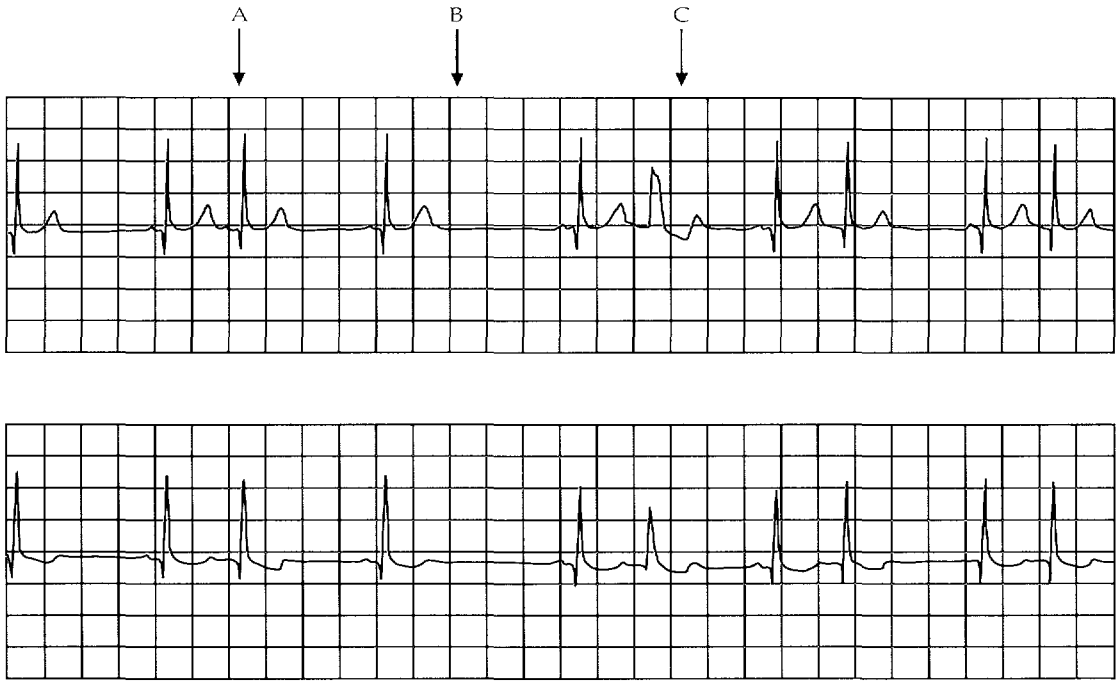


Figure 1.12 — Blocked atrial bigeminy.

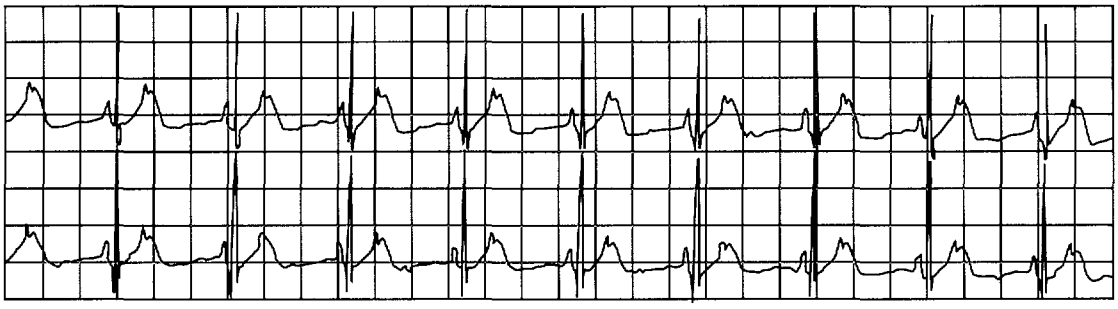
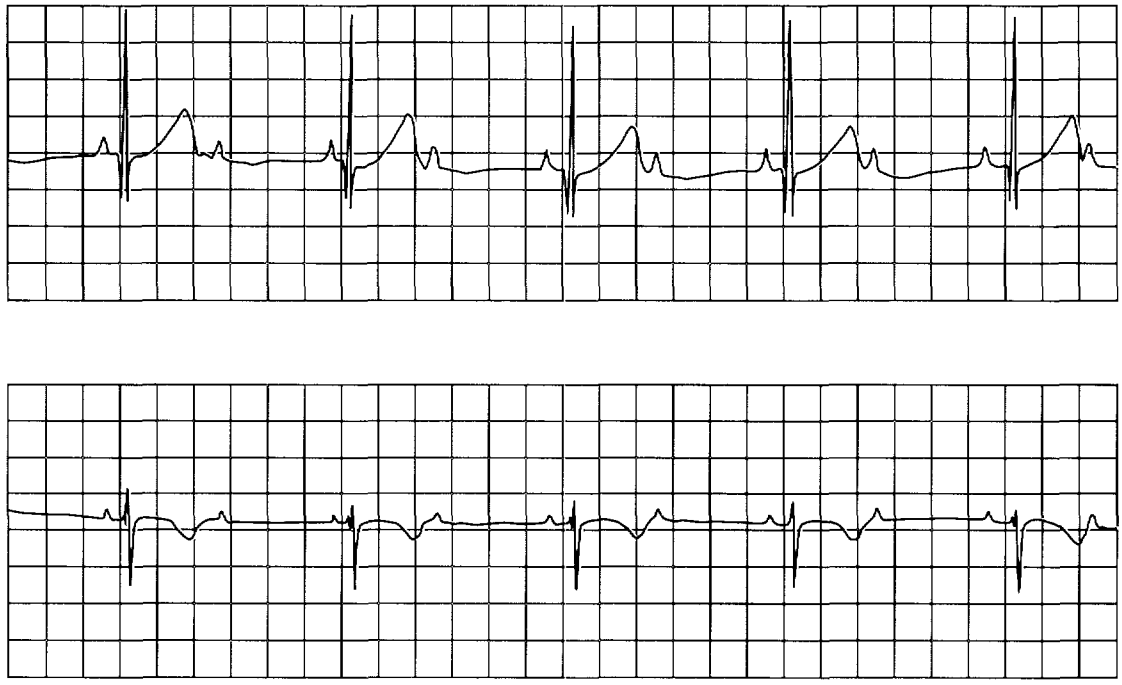


Figure 1.13 — Patient with long QT syndrome and 2:1 AV block.



1.6 Considerations in Neonatal Arrhythmia Therapy

Very little is known about the newborn's ability to metabolize many of the drugs used in arrhythmia therapy. Generally, infants have a longer elimination half-life of anti-arrhythmic agents and require lower initial dosing and frequent monitoring. Traditional drugs such as digoxin, propranolol and procainamide have time-proven use profiles and are relatively safe. While digoxin is the only FDA-approved anti-arrhythmic agent in pediatrics, dosing guidelines are recognized. Newer drugs, such as mexiletine, flecainide, propafenone, sotalol, amiodarone and moricizine are being used with increasing frequency. Of these drugs, flecainide has undergone more scrutiny and testing than any other agent; in pediatric patients with normal hearts, it is safe and effective for SVTs and some forms of ventricular tachycardia (VT). The half-life of flecainide is high at birth (as high as 29 hours in the first hours of life) and gradually declines to 8 to 9 hours by 3 months of age. By 10 years of age, the drug's half life has increased toward a stable adult range of 11 to 12 hours.

Changes in autonomic tone, diet, activity, renal function, hepatic function and body composition likely account for the observation that the first year of life is a time when drug metabolism and disposition are in great flux. Physicians who prescribe anti-arrhythmic agents to young patients need to be aware of each drug's metabolism, the presence of any active metabolites, and the effect these changes have on drug metabolism and excretion throughout early life.

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2.0 NEONATAL BLOOD PRESSURE

Blood pressure is not monitored routinely in the healthy newborn infant. However, in the full-term or preterm infant, blood pressure monitoring is a critical variable in successful neonatal intensive care. The anatomy, physiology, and physics of the adult cardiovascular system and blood pressure measurement have been described in detail in the volume in this series entitled, *Blood Pressure*.[1] In this section, only those theoretical or technical differences which relate to the newborn will be repeated. For the newborn, blood pressure is typically measured by invasive techniques utilizing an intra-arterial catheter in the intensive care setting, or noninvasively using the oscillometric method.

2.1 *Anatomy and Physiology of the Circulatory System*

The cardiovascular system consists of a set of blood vessels through which blood flows and the heart which provides the energy necessary to propel the blood. The entire system forms a closed circuit with the blood continuously pumped out of the heart through arteries and returned to the heart via veins. This circulatory system is composed of two distinct circuits — the pulmonary circulation to the lungs and the systemic circulation to the remainder of the body. Both circuits begin and end at the heart, which is divided longitudinally into two functional halves. The pulmonary circulation receives deoxygenated venous blood pumped from the right side of the heart, transports it to the lungs where it is oxygenated, and returns it to the left side of the heart. The systemic circulation receives oxygenated blood pumped from the left side of the heart and delivers it to all tissues of the body, including the bronchial circulation, returning the deoxygenated blood to the right side of the heart. In both circuits the vessels carrying blood away from the heart are called arteries and those returning blood to the heart are called veins (Figure 2.1).

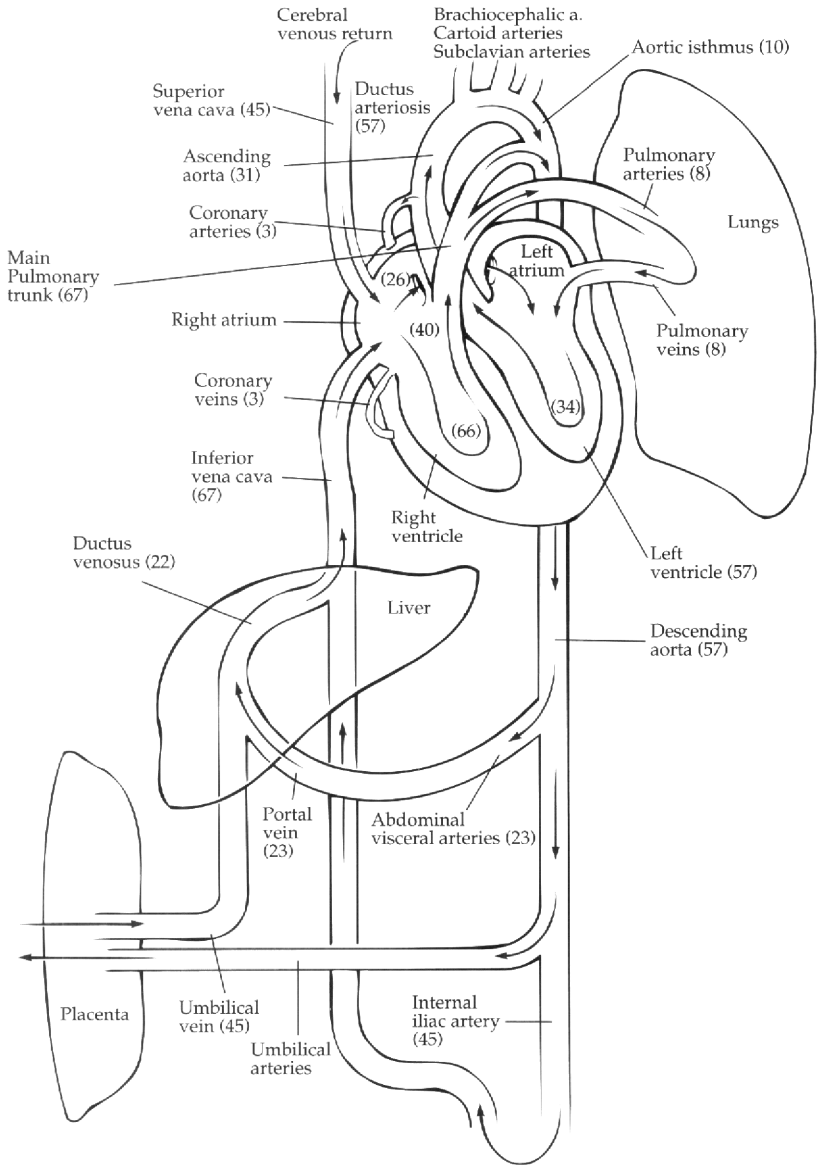
2.1.1 Circulation in the Newborn

The anatomy and physiology of the newborn's circulatory system is similar to a child or adult, except the vessels are smaller and the normal values of blood pressure are lower. In some premature infants, circulatory pathways may be altered (i.e., patent ductus arteriosus, or unclosed foramen ovale).

2.1.2 Cardiac Cycle

The period from the end of one heart contraction to the end of the next is called a cardiac cycle. Each cycle begins with the spontaneous generation of an electrical action potential in the sinoatrial (SA) node, a small mass of specialized myocardial cells embedded in the posterior wall of the right atrium near the opening of the superior vena cava. The SA node serves as the normal pacemaker for the entire heart. The action potential travels rapidly through both the atria, triggering atrial contraction a few milliseconds later. From there it enters the atrioventricular (AV) node, which lies between the right atrium and the right ventricle. The action potential is delayed in the

Figure 2.1 — Diagrammatic representation of the normal fetal circulation and major flow patterns pressure values are in mmHg. (from *Maternal and Fetal Medicine: Principles and Practices*. Creasy RK, Resnick R, Editors. Philadelphia, PA: WB Saunders Co.; 1989.)



AV node for approximately 100 msec to allow the atria to contract and empty their contents into the ventricles before ventricular contraction. Therefore, the atria act as primer pumps for the ventricles. The ventricles thus provide the major source of power for moving blood through the vascular system.

2.1.3 Standard Pressure Definitions

Although the term systolic pressure technically implies the pressure at any instant during systole, it is conventionally used to denote the peak pressure during a cardiac cycle. Similarly, the term diastolic pressure is used to signify the minimum pressure during a cardiac cycle. Pulse pressure is the difference between systolic and diastolic pressure. Pulse pressure may be increased (widened) in the presence of cardiovascular abnormalities in which blood leaves the systemic arterial system through an abnormal pathway, such as a patent ductus arteriosus or an arteriovenous fistula.

Mean pressure is the average pressure during a cardiac cycle. It can be derived by integrating the blood pressure over time, or by use of a low-pass filter (ω_{cutoff} = 0.05 Hz). If systolic and diastolic pressures are known, the mean pressure can be approximated using the following formula:

$$\text{Mean pressure} = \text{diastolic pressure} + \text{pulse pressure}/3$$

It should be recognized that the above equation may, at times, be inaccurate if the pressure upstroke is unusually rapid (hypercontractile state) or aortic runoff is accelerated (widened pulse pressure) as explained above.

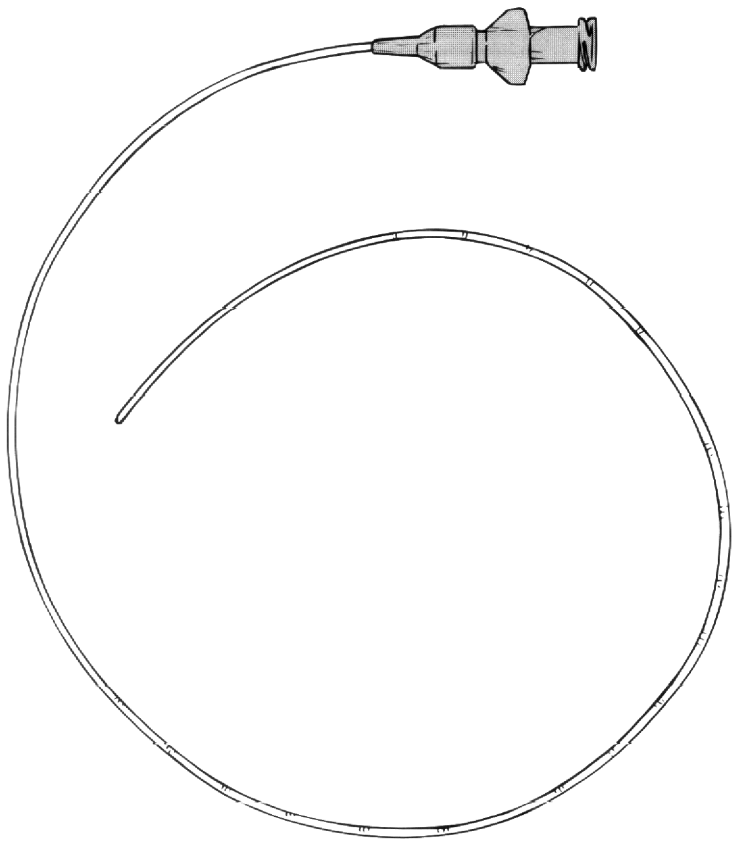
2.2 *Measurement Techniques*

2.2.1 Invasive Arterial Blood Pressure

In the newborn, the two most common sites for arterial entry for invasive pressure measurement are either the umbilical artery (obviously not available in the child or adult) or the radial artery. The posterior tibial artery is less commonly used. Present-day umbilical artery catheters have both end and side holes (Figure 2.2). The presence of an end hole pointing upstream in the arterial system may introduce an artifactually higher blood pressure value related to the pressure component caused by kinetic energy.[2] The magnitude of the artifact is typically very small (less than 1 mmHg) and may be ignored. Because of the size of newborn's arteries, the clinician needs to assess the risk of complications prior to placing a direct blood pressure monitoring catheter. The risks for vascular thrombosis, local or generalized infection, and excessive blood loss may be unacceptably high. In addition, because of the small size of the newborn's arteries, care must be taken to ensure adequate heparinization to prevent catheter and/or vessel clotting.

The newborn has a blood volume of about 80 ml/kg. Thus, the 3-kg infant has a total of only 240 ml intravascular blood volume. Flush solution rate of infusion must be controlled carefully to avoid circulatory overload.

Figure 2.2 — Umbilical artery catheter.



2.2.1.1 Electrical System

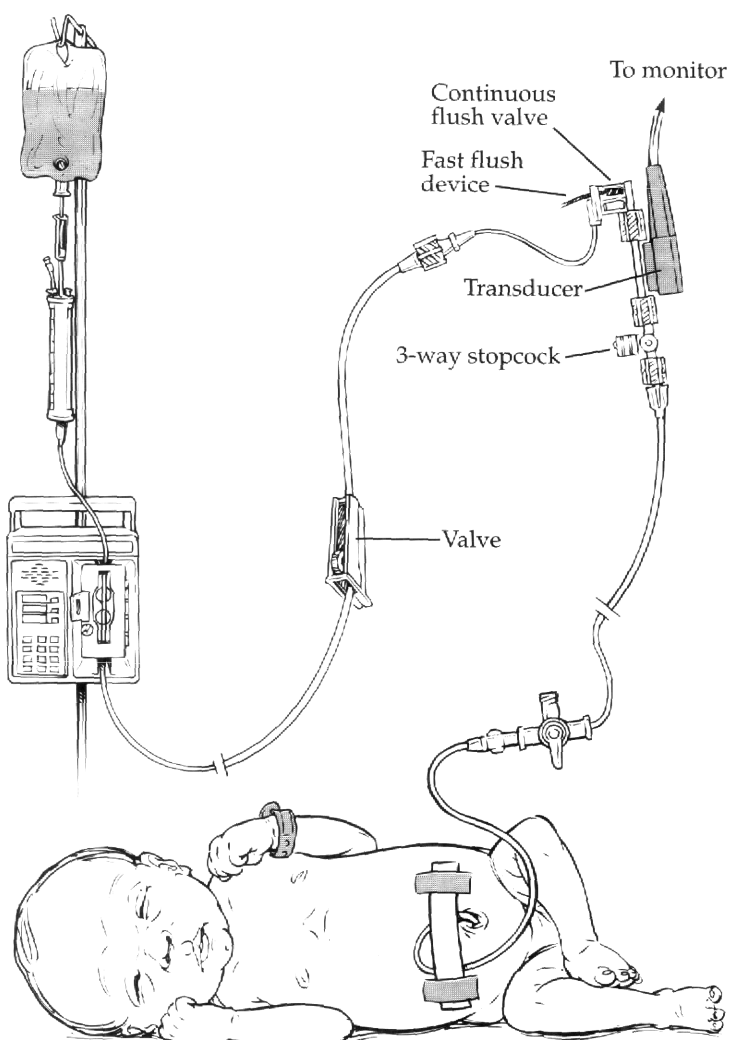
The components of the electrical system consist of the amplifier, the monitor, the processor, and the recorder. The amplifier increases or amplifies the signal from the transducer and is displayed on the monitor as a pressure waveform and numerically on the digital display. The recorder documents the pressure waveform on paper. The components of the electrical system are used for processing and displaying pressure waveforms and for obtaining derived hemodynamic parameters (e.g., vascular resistance or stroke work). The same electrical components are used for monitoring neonatal and adult invasive blood pressure.

2.2.1.2 Fluid-Filled System

The components of the fluid-filled system carry the mechanical signal from the patient's vascular system to the transducer. These components consist of the vascular catheter, the noncompliant pressure tubing (< 4 feet), a flush device that allows continuous and manual flushing of the catheter tubing system, two or three stopcocks, a pressure transducer that converts fluid pressures to electrical voltage, an infusion

pump, and a flush solution of normal saline which usually contains heparin to maintain catheter patency (Figure 2.3); the amount of heparin added to the solution varies depending on institutional protocol. The plastic components are disposable and should be discarded after 48 to 72 hours of use to minimize the risk of infection. The main difference between the adult and neonatal fluid system is the technique to prevent circulatory overload. A pressure bag inflated to 300 mmHg is used for the adult system and an infusion pump (maximum pressure of 100 mmHg) is used for the neonatal system. The fast flush device and continuous flow valves are designed to deliver very small fluid volumes, to avoid circulatory overload.

Figure 2.3 — A representation of an arterial monitoring set-up.



2.2.1.3 Sources of Errors in Invasive Blood Pressure Measurements

The sources of error of measurement of invasive neonatal blood pressure, such as air in the connector tubing or stopcocks, and height of the transducer with respect to height of the heart, are of critical importance and must be monitored frequently.

Knowledge of the dynamic response of a direct measurement system ensures accurate interpretation of the obtained readings. The frequency response of a measurement system generally can be defined by the determination of two parameters — the damping ratio (β) and the natural frequency (ω_0). If the value of either of these parameters fall outside of acceptable ranges ($\omega_0 > 20$ Hz and β near 0.7), distortion of the measurement may result. The dynamic response characteristics of the catheter-tubing-transducer system is compromised by the presence of air bubbles, pressure tubing that is more than four feet in length, and use of compliant, distensible tubing. Note: more information about the frequency response is available in *Blood Pressure*.[1]

Other causes of inaccurate blood pressure readings are loose connections, accumulation of blood in and around the transducer, blood clots, and an improper reference point.

2.2.2 Noninvasive Blood Pressure

The routine for blood pressure measurement in the newborn is for arm or leg cuff placement. Because distances from the heart to the arm or leg do not differ by many centimeters, no clinically significant difference in blood pressure measurement should result if either is utilized. For the newborn, no studies have been published comparing more than one noninvasive method with a reference standard intra-arterial pressure; it is therefore not possible now to comment on the relative accuracy of various noninvasive methods.

2.2.2.1 Korotkoff Sounds

Korotkoff sounds are not usually audible in the neonate because the energy within the vessel may be insufficient to produce an audible sound at the skin surface. The small arm size can be a limiting factor in relation to stethoscope head size, making it difficult to position properly or use the stethoscope. If Korotkoff sounds are present, there may be no phase V; sounds never disappear during cuff deflation.[3,4] Because of these technical problems of auscultation, this technique is not routinely used in the measurement of neonatal blood pressure.

2.2.2.2 Flush Technique

Because the flush technique is inaccurate in the presence of anemia, hypothermia, or edema, it is not routinely used.[3] The first step in the flush technique is to wrap a cuff of suitable size around either an arm or leg. The limb is raised and then wrapped

tightly with elastic bandage to drain it of blood. The cuff is then inflated to suprasystolic pressure and the limb is lowered to heart level. The bandage is removed and the cuff pressure is gradually reduced until the limb flushes. This blood pressure value corresponds to the mean arterial pressure.

2.2.2.3 Palpation

Another technique not routinely used is that of direct palpation of the distal pulse. The cuff is inflated to suprasystolic levels and gradually reduced until the clinician is able to palpate the pulse peripheral to the cuff. Because of the lack of cooperation of neonates and the very small vessel size, a great deal of experience is necessary to develop skills to measure blood pressure accurately with this technique. Some clinicians' sensory abilities may not be sufficiently sensitive to allow readings which can be used in the care of the newborn.

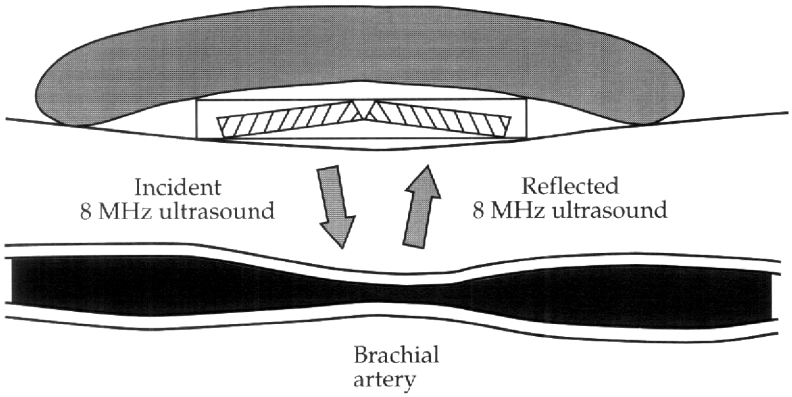
2.2.2.4 Doppler Ultrasound

The Doppler ultrasound method employs two piezoelectric crystals placed under or distal to the occluding cuff directly over the artery to be compressed. Small ultrasonic frequency shifts can be measured when turbulent flow in the vessel causes vessel wall vibration. Frequency shifts are absent when there is no flow in the arteries (e.g., when the cuff is inflated to suprasystolic pressures). Normal flow results in little arterial wall motion or frequency shift. Therefore, when the cuff pressure falls below diastolic blood pressure, frequency shift becomes reduced (Figure 2.4). The Doppler ultrasound measurement of blood pressure works in extremely noisy environments but requires precise placement of the cuff and transducer. This technique has been found to give clinically acceptable values for systolic blood pressure, and "reasonable diastolic readings."[5] Other researchers were unable to detect diastolic values using Doppler ultrasound (Figure 2.5).[1,5] Several studies have used this technique to determine blood pressure in the neonatal population.[6]

2.2.2.5 Oscillometry

The most widely-used method of blood pressure measurement is by the oscillometric technique (Figure 2.6). This method has distinct advantages because it does not depend upon the transmission or detection of Korotkoff sounds, and can be used in a noisy critical care environment. The only disadvantages of the system are the spontaneous movement of the awake neonate and the inaccuracies from respiratory artifact or irregular cardiac rhythms. Oscillatory pressure changes can be noted from above systole, gradually increasing as the pressure drops, until they reach a maximum at the mean blood pressure. They then decrease until below the diastolic pressure. Functions of the changes in amplitude of these pressure waves are used to determine the systolic and diastolic blood pressures. These oscillations can be detected in the transducer monitoring cuff pressure. The point of maximal oscillation corresponds to mean blood pressure (Figure 2.6b). Systolic and diastolic blood pressure values are then determine using a proprietary algorithm.

Figure 2.4 — Illustration of the principle of indirect blood pressure measurement with Doppler-shifted ultrasound. Each movement of the reflecting surface (the arterial wall) generates a characteristic Doppler-shift at the instrument output.



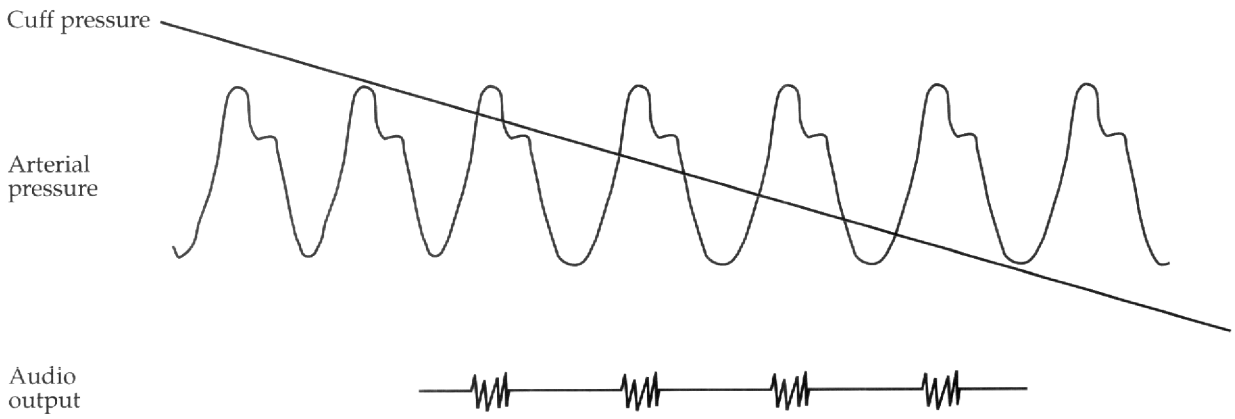


Figure 2.5 — Simultaneous recording of subclavian pressure, intrabladder pressure, and Doppler signal. (from Steinfeld L, Dimich I, Rader R. Pressure in the pediatric patient. *J Pediatr*. 1978;92:934.)

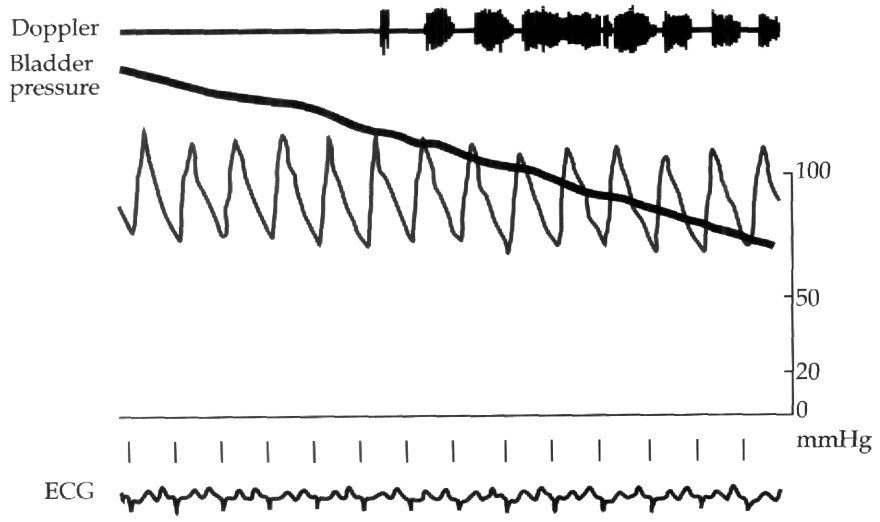


Figure 2.6a — Oscillometric method.

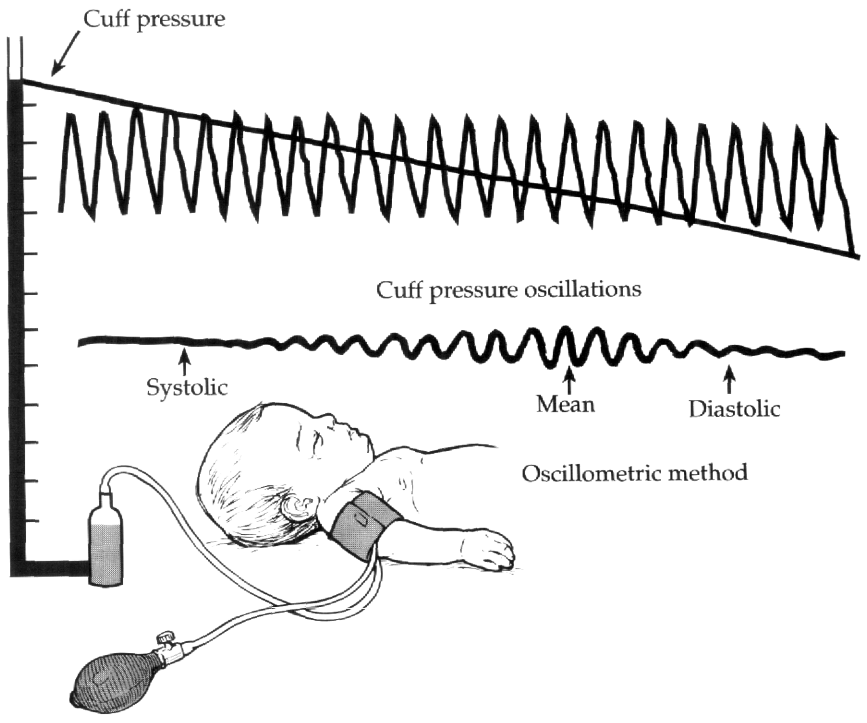
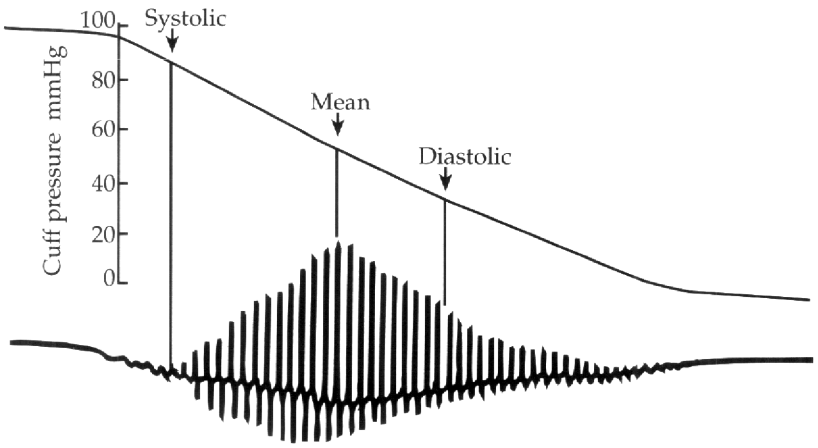


Figure 2.6b — Oscillometric method.



The accuracy of the oscillometric technique has been demonstrated in several laboratories.[7-12] In most of these studies the accuracy was determined in comparison to intra-arterial catheters, usually in the umbilical artery. It should be noted that this method of standardization is markedly different from the process in adults, in which oscillometric readings are frequently compared to central aortic pressures or auscultatory determinations using Korotkoff sounds at the brachial artery. As discussed above, neonatal blood pressure cannot be determined with any certainty by the use of Korotkoff sounds. There have been some data collected, however, which brings into question the accuracy of an oscillometric device in the detection of hypotension in very low birthweight (700 g to 1470 g) infants.[13] In this clinical situation, the physician should only use blood pressure measurements from direct intra-arterial catheters.

2.2.2.6 Sources of Error in Noninvasive Blood Pressure Measurements

In the November 1993 American Heart Association Special Report,[3] 0.4 was recommended as the optimal ratio of cuff bladder width to arm circumference. This led to a recommended bladder width of 3 cm and a length of 6 cm for arm circumferences of 6 cm. In the Task Force Report,[4] the recommended newborn cuff width was 2.5 cm to 4 cm, with a length from 5 cm to 9 cm. Width has the greatest effect on reading accuracy. The length of the bladder should be such that it completely encircles the circumference of the neonate's limb, as opposed to an 80% encirclement for adults.

Several studies have questioned the bladder width — arm circumference ratio of 0.40. Lum and Jones[14] found that cuff width effect was minimized at a ratio of 0.50. In a series of studies by Steinfield, Cohen, and co-workers the authors noted that, as expected, cuffs which were relatively narrow gave higher systolic values than intra-arterial pressures, but no "wide-cuff effect" was noted (i.e., measured systolic blood pressures were not lower than the reference values).

The normal neonatal values of blood pressure are considerably lower than those in adults. Therefore, from a technical/mechanical standpoint, the clinician should be certain that the blood pressure monitor does not use a very rapid bleed rate. A bleed rate that is too fast does not allow the apparatus to detect the oscillations frequently enough at each level of blood pressure, and will result in a very high "percentage" error. A systolic blood pressure error of 8 mmHg in the newborn represents a 10% error, while in the adult it will be an error of about half that magnitude.

Because newborns cannot be asked to hold their limb still during blood pressure measurement, excessive or prolonged cuff inflation will usually lead to the newborn crying and moving, both of which will impair accuracy. Crying produces a Valsalva maneuver that will raise systolic blood pressure greatly, and motion may lead to the inaccurate estimation of both systolic and diastolic blood pressure if the monitor interprets the infant's motor movements as vessel oscillations.

2.3 Normal Blood Pressure Values

As pointed out by McGarvey and Zinner, it is critically important to obtain blood pressure values in the same sleep/activity status as the reference standards which the physician desires to use for comparison. It has been consistently noted that blood pressure values are 7 mmHg to 10 mmHg higher in awake than asleep newborns.[5]

There are a small number of studies available which have determined normal blood pressure values in moderate to large numbers of newborn infants.[19-24] The largest of these were combined for the production of the curves presented in the Task Force Report.[4] As shown in Table 2.1, systolic blood pressure rises rapidly during the first month of life, especially during the first week of life. After 2 months of age (outside of the newborn period) the systolic blood pressure becomes stable for the remainder of the first year. Diastolic blood pressure slowly decreases during the first few weeks, and begins to rise at approximately 3 months of age. The data tabulated in the Task Force Report[4] are primarily seeking to define the distinction between normal blood pressure and elevated blood pressure (hypertension). The lower end of the blood pressure spectrum (hypotension/shock) are less well defined, but generally are very low in comparison to adult values. Refer to the Task Force Report for more information on the different evaluation and treatment of elevated blood pressure in the newborn.

There have been additional studies of blood pressure in the preterm, low birthweight, and immediate newborn. Versmold et al.,[25] published regression diagrams for blood pressure values during the first 12 hours of life, a time period not well studied in the Task Force Report. These regressions (Figure 2.7) show that babies under 1 kg in weight can have a blood pressure of 30/15 mmHg and be perfectly normal.

Table 2.1 — Normal Newborn Blood Pressure Values (mmHg).

Phase	Gender	Age	Blood pressure (mean±SD)	N
Systolic	Male	< 7 days	72.7±9.6	1436
		8 days to 1 month	82.0±11.1	334
	Female	< 7 days	71.8±9.3	1 365
		8 days to 1 month	81.1±12.0	352
Diastolic	Male	< 7 days	51.1±8.9	480
		8 days to 1 month	50.3±11.2	329
	Female	< 7 days	50.5±8.4	489
		8 days to 1 month	50.7±11.5	341

Figure 2.7(a) — Age-specific percentiles of blood pressure measurements in boys - birth to 12 months of age; Korotkoff phase IV (K4) used for diastolic blood pressure. (from Horan MJ. Report of the second task force on blood pressure control in children - 1987. *Pediatrics*. 1987;79:5-6.)

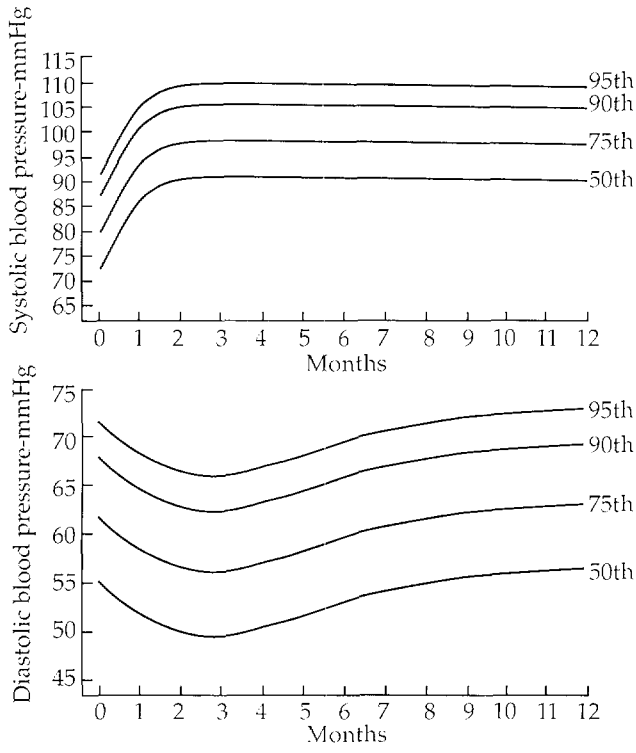
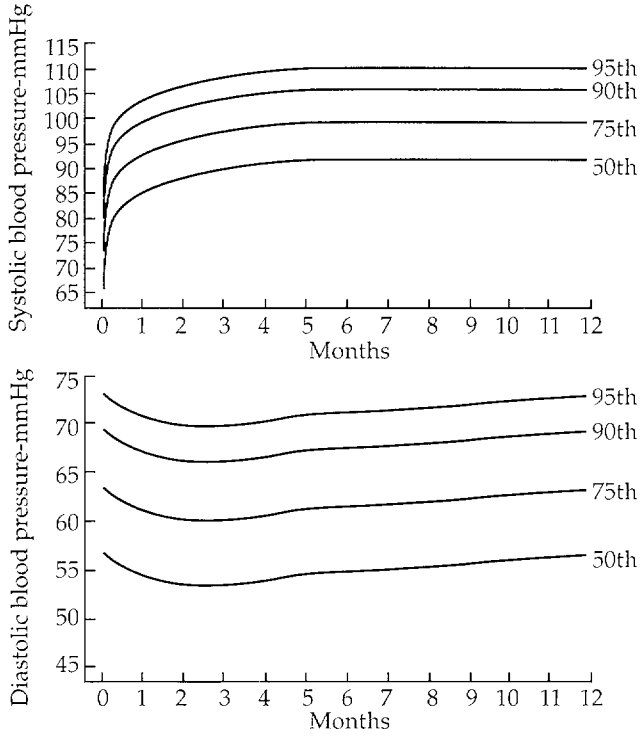


Figure 2.7(b) — Age-specific percentiles of blood pressure measurements in girls - birth to 12 months of age; Korotkoff phase IV (K4) used for diastolic blood pressure.



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3.0 INFANT WARMING/TEMPERATURE MONITORING

3.1 History and Basic Physiological Principles

An understanding of the mechanisms of homeothermic adaptation in the newborn and the application of this knowledge to thermal support of sick and the preterm infants is one of the foundation stones of modern neonatal medicine. The recognition of the need to protect the very young against heat loss can be dated to at least ancient Egypt, where sophisticated methods of incubation were developed for hatching chicken eggs.[1] These early methods were the forerunners of the convective incubators and radiant warmers, which are currently used in neonatal medicine for controlled heat delivery to newborn infants.

The modern history of neonatal temperature control began in the late 19th century with the observation by Pierre Budin at Paris Maternity Hospital that, following introduction of temperature control measures, mortality rates decreased from 66% to 38% in infants with birth weights less than 2000 gms (see Figure 3.1).[1] In 1957, Silverman reported that the survival of premature infants in the first days of life was higher when the relative humidity was maintained at 80% to 90%.[2] During this study it was noted that the mean body temperature of infants maintained in humidified environments was significantly higher than the mean body temperature of infants in incubators with lower relative humidity (30% to 60%). This observation led to the formulation of the normothermic hypothesis which stated that the survival of preterm infants would be favorably influenced by environments which maintained normal body temperature.

In terrestrial mammals, birth marks a transition from an environment that is warm and wet to one that is relatively cold and dry. Preterm low-birth-weight infants are ill equipped to make this transition and are prone to cold stress, metabolic acidosis, and the development of hypothermia. Low body temperature is inversely related to survival and every effort must be made to maintain infants within the thermoneutral zone (TNZ) (see Figure 3.2). The TNZ represents the environmental temperature range within which an infant has a normal body temperature and a minimal basal metabolic rate. The TNZ varies with chronological age and spans a lower temperature range in adults (25ºC to 30ºC) than in full-term infants (32ºC to 34ºC). Preterm infants exhibit an elevated, narrow, and changing TNZ during the first few days following birth. Infants cared for outside their TNZ exhibit slower growth rates than infants with the same caloric intake maintained within their appropriate zone. Recognition of the importance of this concept led to the establishment of scopes charts for preterm infants.[3] Ideally, maintenance of the TNZ in thermoregulated infants will reduce the need to direct calories away from growth to heat-producing metabolic activity and will obviate the need to rewarm infants who become hypothermic.

Figure 3.1 — Tarnier's closed (convective) incubator (1890). The design for this incubator was first developed by the French physician Stephane Tarnier. The incubator had a hot water reservoir beneath the bed that heated the surrounding air to maintain an ambient temperature of 29ºC to 30ºC. It had a double glass cover to allow visual monitoring and could accommodate two infants.

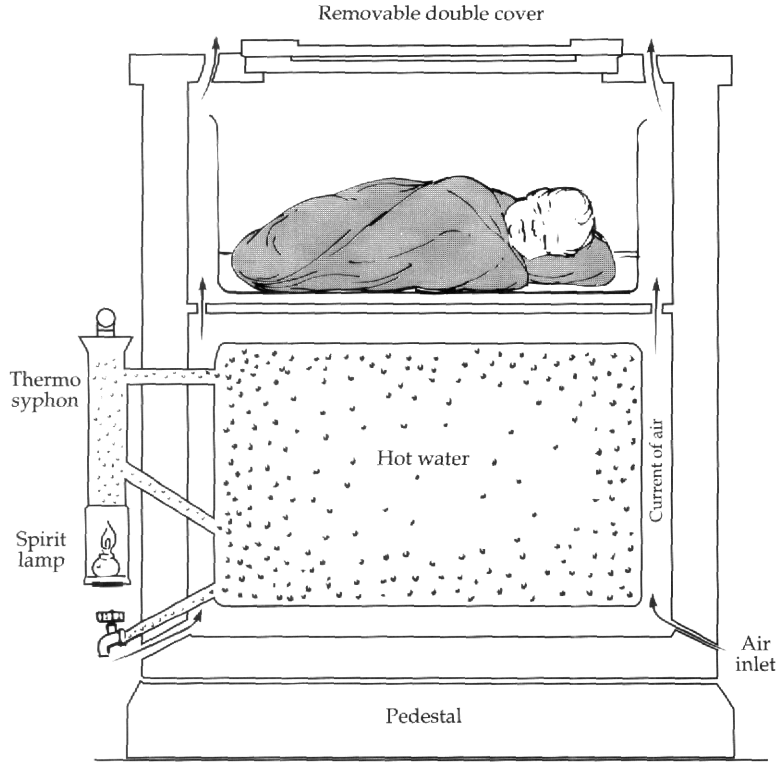
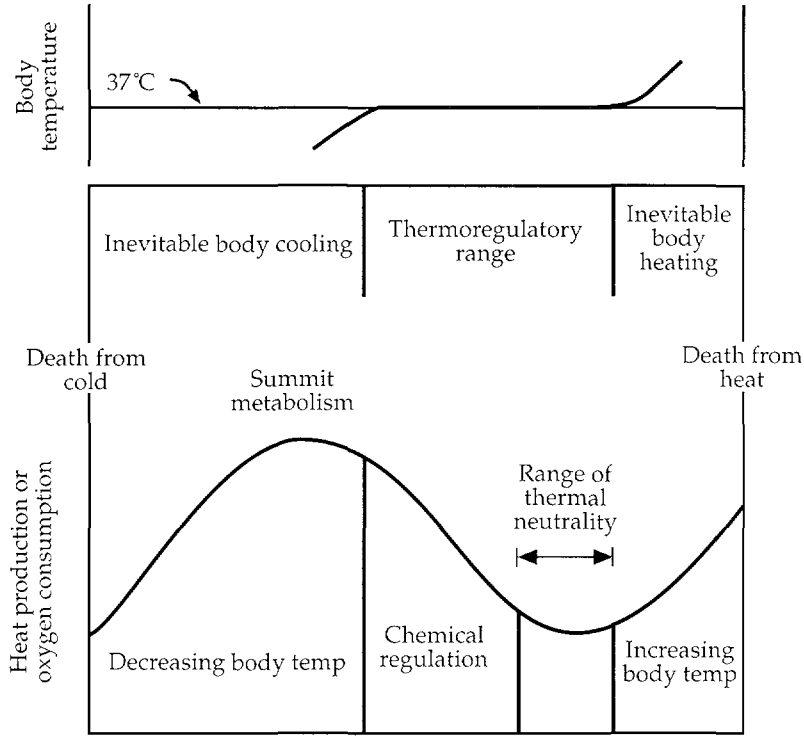


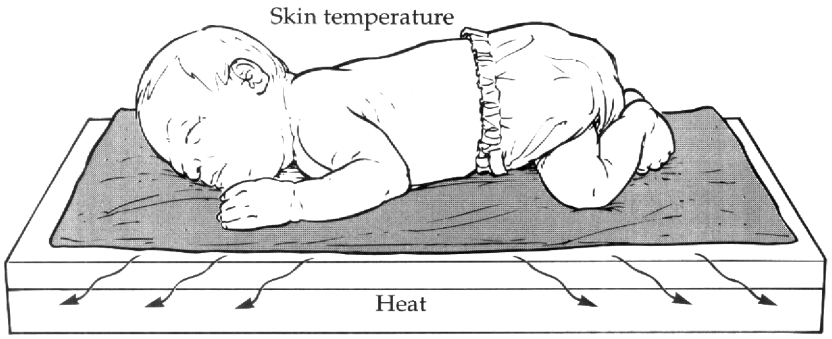
Figure 3.2 — Range of thermal neutrality and the effects of environmental temperature on oxygen consumption and body temperature. It is desirable to maintain preterm infants in a thermal environment in which their basal metabolic rate is minimized as indicated by their systemic oxygen consumption (lower curve) and normal body temperature (upper curve). (from Klaus MH, Fanaroff AA, Martin RI. The Physical Environment. In: *Care of the High-Risk Neonate*. Klaus MH, Fanaroff AA, Editors. Philadelphia, PA: WB Saunders Co.; 1986.)



3.2 Physics of Heat Transfer

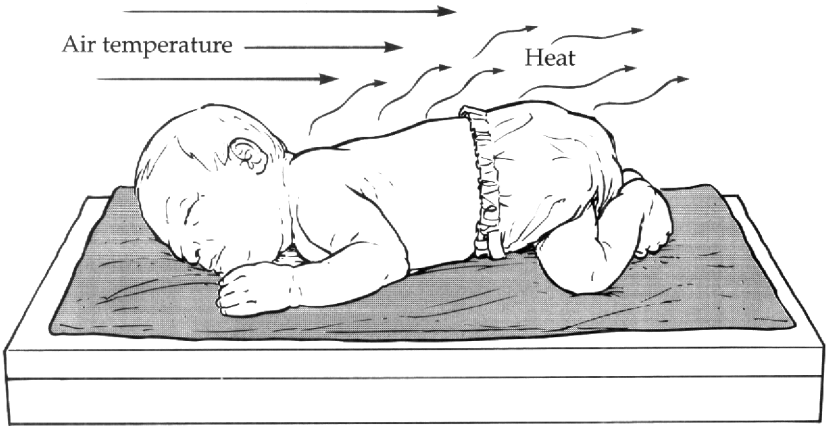
The choice of the appropriate method for newborn temperature control requires a basic understanding of heat transfer methods. The newborn infant, whether term or preterm, like any physical object, loses heat to the environment by four different modes (see Figures 3.3 to 3.6):[4]

Figure 3.3 — Heat transfer by conduction is from the baby to the underlying mattress. The estimated surface area for this heat loss is approximately 10% of the infant's surface area. (from Leblanc MH. Neonatal heat transfer. In: *Fetal and Neonatal Physiology, Volume One.* Polin R, Fox W, Editors. Philadelphia, PA: WB Saunders Co., 1992.)



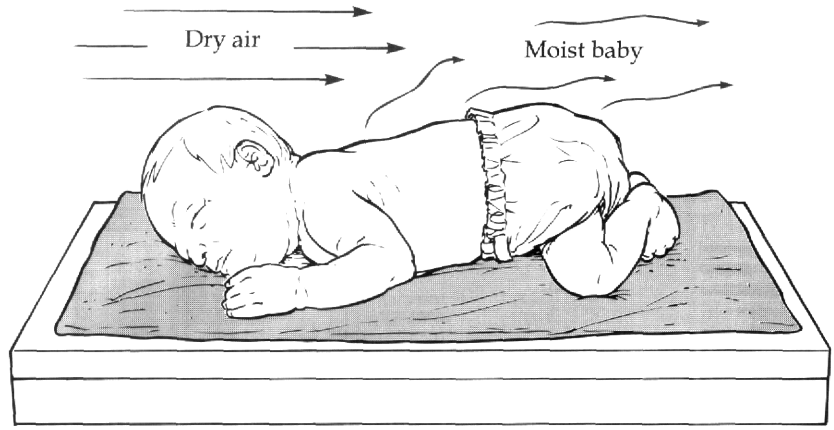
Conduction

Figure 3.4 — Heat transfer by convection to the air surrounding the infant. The heated air expands and moves upwards or is circulated by the incubator's fan. (from Leblanc MH. Neonatal heat transfer. In: *Fetal and Neonatal Physiology, Volume One.* Polin R, Fox W, Editors. Philadelphia, PA: WB Saunders Co., 1992.)



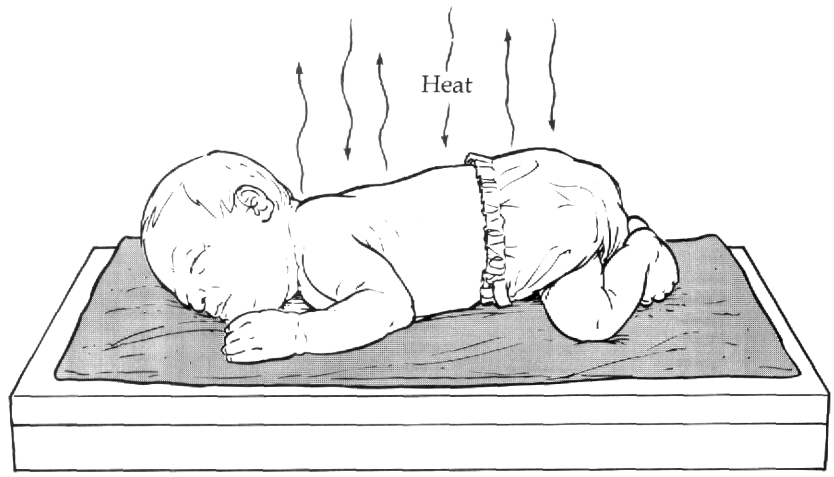
Convection

Figure 3.5 — Heat transfer by evaporation entails diffusion of water molecules from the skin surface. (from Leblanc MH. Neonatal heat transfer. In: *Fetal and Neonatal Physiology, Volume One.* Polin R, Fox W, Editors. Philadelphia, PA: WB Saunders Co., 1992.)



Evaporation

Figure 3.6 — Heat transfer by radiation occurs in the form of electromagnetic energy and is dependent on temperature differences between the body and solid objects facing it. (from Leblanc MH. Neonatal heat transfer. In: *Fetal and Neonatal Physiology, Volume One.* Polin R, Fox W, Editors. Philadelphia, PA: WB Saunders Co., 1992.)



Radiation

3.2.1 Conduction

Conduction is defined as the transfer of energy from the molecules of a body to the molecules of a solid object in contact with that body. In newborn intensive care units, infants usually recline on a flat mattress. The heat flow through the mattress by thermal conduction is

$$H = kA\, dT/dx$$

where
- H = heat flow
- k = a thermal conductivity constant for the particular mattress and its coverings
- A = the area through which the heat flows
- dT/dx = the change in temperature per unit distance through the solid.

Preterm infants have about 10% of their surface area in contact with the mattress. A 2.5 cm-thick mattress (closed-pore foam rubber type) has a thermal conductivity of approximately 0.9 watt/m^2/ºC. An approximation of conductive heat loss calculated on total heat production of 1.7 watts/kg shows that only about 0.5% is conducted through the mattress, or 0.012 watt/ºC for a 1500 gm infant. Thus, conductive heat losses are generally regarded as minimal in usual infant care situations.

3.2.2 Convection

Convection is the transfer of thermal energy from the molecules of the body to the molecules of an adjacent gas. This heated gas expands (Boyle's law) and is displaced upwards by the force of gravity of the cooler and more dense surrounding gas; this gas movement is called free convection. Away from the infant's skin, air currents in the nursery or those produced by the incubator's fan will result in turbulence and mixing of the hot gas with the surrounding air (forced convection). Convective heat losses in infants have been measured and calculated to be between 3.1 watts/m^2/ºK to 8.5 watts/m^2/ºK, or, in one study, approximately 40% to 50% of nonevaporative heat losses.[5]

3.2.3 Evaporation

Evaporation is defined as the total heat transfer by energy-carrying water molecules from the skin and respiratory tract to the drier environment. Evaporation is affected by gestational age as well as postnatal age and by the differences in partial pressures of water vapor next to the skin and in the surrounding air. In the term infant and the older child, the outermost layer of the skin, the stratum corneum, serves as a barrier to evaporative heat loss unless covered with amniotic fluid or after a bath. The skin of the premature infant less than 28 weeks gestation constitutes a poor barrier to heat loss by evaporation due to immature formation of the stratum corneum. In addition to a poor epidermal barrier to water transport, the velocity of the air surrounding the skin has a large effect on evaporative heat losses in the preterm infant. In very low birth-weight infants, during the first days of life, evaporative heat losses exceed all other sources of heat loss and often exceed total heat production.

3.2.4 Radiation

Radiant heat loss is defined as the net rate of heat loss in the form of electromagnetic waves between the body and the environmental surfaces not in contact with the body (e.g., the walls of the incubator). Radiant heat loss is dependent on a number of factors including the temperature of the skin, the relative surface area and geometry of the exposed body part, the distance and angles to irradiated objects (such as the incubator walls or nearby windows), the emissivity of the infant's skin, and the emissivity of the irradiated objects. Based on studies in adults, emissivity is defined as the ratio of the total radiant energy emitted by a body to the energy emitted by a full radiator (maximal radiant output) at the same temperature. Typically, adult human skin is given the value of 1, although no data exists regarding the emissivity of the skin of a preterm infant. In general, radiant heat loss is not dependent on the air temperature. Therefore, it is possible for an infant to be cold stressed despite an air temperature higher than skin temperature if the walls or windows are sufficiently cold. In contrast, an infant in an incubator with a relatively cool air temperature may get hyperthermic if the walls are too hot.

3.3 *Temperature Sensor Technology*

Mercury-in-glass thermometers remain the most common method of temperature measurement in healthy full-term infants. They are accurate and inexpensive, and are used for routine clinical measurements. The need to continuously measure skin or air temperatures in order to servocontrol heater power outputs for environmental control has resulted in the introduction of various temperature transducers into clinical practice.[6] The most widely used device to measure and control the thermal environment in newborn infants is the thermal resistor (thermistor).

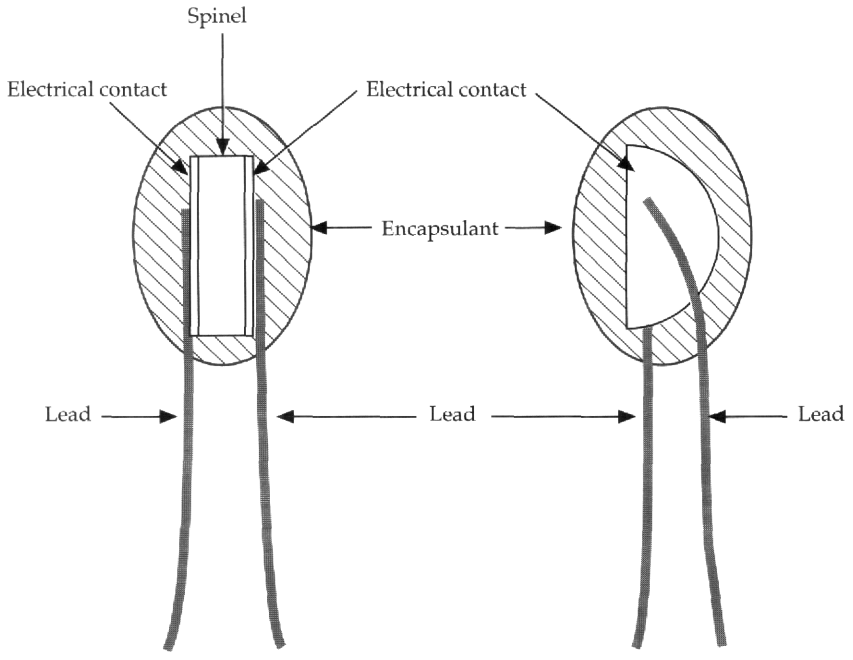
A thermistor is a semiconductor with a large coefficient of resistance (see Figure 3.7).[7] Most thermistors are made from combinations of metal oxides (e.g., manganese, nickel, copper). They are usually of the negative thermal coefficient (NTC) type, which exhibits a drop in resistance when the temperature rises. When a thermistor is operated at a power level that is low enough to produce insignificant self-heating they are referred to as zero-power resistors. Each thermistor has a temperature coefficient, which is the ratio between the rate of change in resistance with temperature to the resistance of the thermistor at a given temperature:

$$a = (dRo/dT) / Ro$$

where a = temperature coefficient
Ro = resistance of thermistor
dRo/dT = the rate of change in resistance.

For temperature measurement, the resistance is measured over a resistance bridge where R_1, R_2 and R_3 are known (see Figure 3.8a). Since the current will be inversely proportional to the resistance, it is easy to calculate the actual resistance of the thermistor. A different way is to use a known voltage source and measure the voltage in reference to the known voltage (see Figure 3.8b).

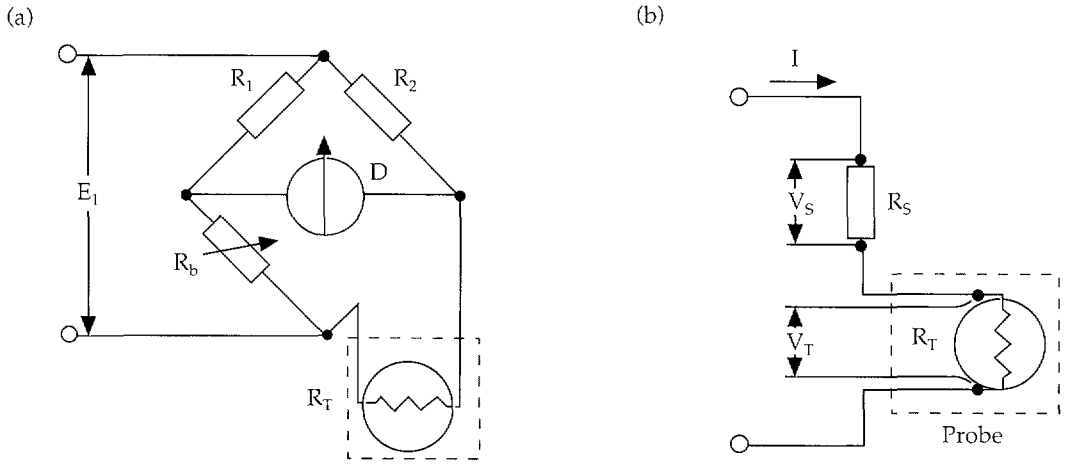
Figure 3.7 — Schema showing the internal construction of a typical thermistor. (from *Temperature Sensors & Probes*. Yellow Springs, OH: YSI Inc.)



Other types of temperature sensors include thermocouples, liquid crystals, and infrared detectors. Thermocouples are durable, stable, inexpensive, and have fast response times, making them especially popular for research purposes. Liquid crystal and chemical strip indicators have been used for chromatic display of surface temperatures in newborns. Another technique based on infrared thermometry that has become widely available for home use is an ear canal temperature transducer. However, the accuracy, coefficient of variation, and general usefulness of this method in preterm and term infants has been questioned.[8] Techniques using diodes and transistors, crystal resonators, and microwave radiometers have a variety of properties and accuracy levels but have not become commonplace for thermal management purposes in clinical neonatology.

Recently, zero-heat flow thermometers have been investigated for noninvasive transcutaneous measurement of body temperature in preterm infants.[9,10] These surface-based thermistor systems are founded on the principle that, under steady state, any body which has an internal heat-producing component will have a continuous flow of heat to its surface as long as the surface is cooler than its internal component. Insulation of the surface thermistor will lead to zero heat flow between the core and the periphery, thereby allowing core temperature to be obtained from the skin. This principle forms the basis for axillary measurements of core body temperature using mercury-in-glass thermometers. Newer methods have been validated in newborn animal models and infants which allow continuous transcutaneous monitoring of core body temperature using well insulated surface thermistors (see Figure 3.9).

Figure 3.8 — Illustration of different thermistor-based measurement methods. (a) A null-balance Wheatstone bridge consists of two fixed resistors (R_1 and R_2), a changing resistor (R_b), and an unknown fourth resistor (R_t); (b) Using the voltage method for temperature measurement, current (I) is determined from the voltage (Vs) across a fixed resistor (R_s) using Ohm's law. (from *Encyclopedia of Medical Devices and Instrumentation: Volume 4*. Webster J, Editor-in-Chief. New York, NY: John Wiley & Sons, Inc.; 1988.)



3.4 Factors that Affect Temperature Accuracy

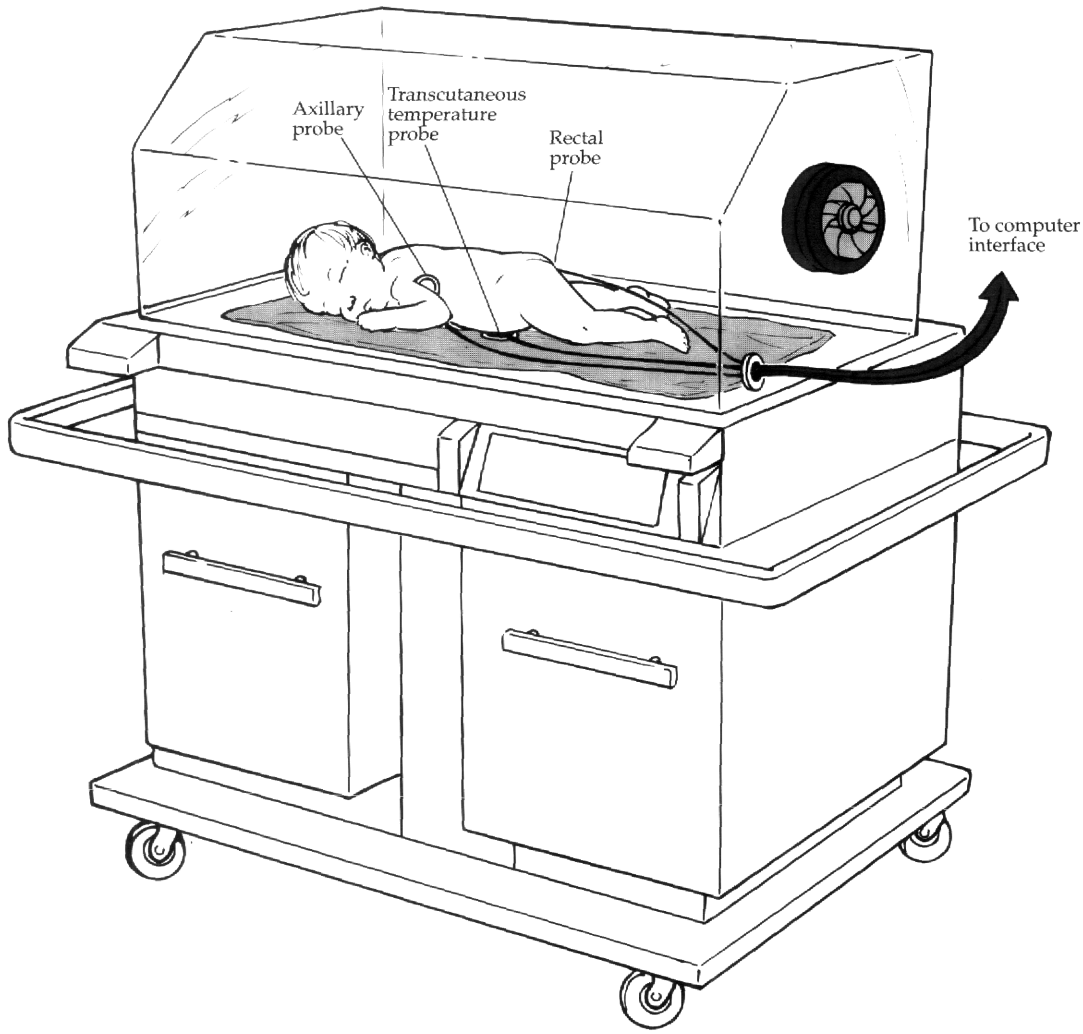
3.4.1 Sensor Microenvironment—Physical Factors

The microenvironment of the thermistor may be very different than that of the surrounding skin. A common observation is that when the position of the baby is changed and the thermistor is sandwiched between the mattress and the skin, an artificially high skin temperature will be recorded. This can result in an inadvertent decrease in heater power output under conditions of skin servocontrol. Similar observations, but to a lesser degree, are noticed when the thermistor is covered with a diaper, or even with the baby's hand.

Other factors affecting the thermistor microenvironment include how the thermistor is attached to the skin. Use of an insulated foam rubber disk (commonly used to shield thermistors from energy emitted by a radiant warmer) results in higher temperature readings compared to thermistors secured with noninsulated clear tape.[11] The water content of the air may also affect skin temperature. A low relative humidity inside a convective incubator, for example, has been shown to decrease body temperature by 1ºC.[12] Contact pressure applied directly to the skin is linearly related to the temperature measured by the thermistor and varies according to body site.[13,14]

The size of the thermistor probe is a major determinant of its time constant a factor that may be important if rapid temperature readings are required. If an instantaneous change in temperature occurs, the time constant is defined as the time to reach $(1\text{-}e^{-1})$ of the target temperature. The smaller the probe head, the shorter the time constant, and hence, the earlier that changes in body temperature will be detected.

Figure 3.9 — Schematic diagram for continuous transcutaneous core temperature measurement.



3.4.2 Sensor Microenvironment — Biological and Physiological Factors

The thermal conductivity of the skin is directly related to cutaneous blood flow.[15] Vasoconstriction of the periphery, e.g., the hands and feet, decreases the temperature of the limbs and is an important mechanism of heat conservation. This phenomenon underlies the common observation of acrocyanosis, or blueness of the hands and feet, in the newborn. Vasodilatation of the periphery has the opposite effect. A warm environment may trigger autonomic activation of eccrine sweat glands with resultant

cooling of the skin surface by evaporation. For the newborn, evaporative heat loss may be disadvantageous during the immediate period following birth, and mechanisms appear to have evolved to protect the infant during this vulnerable period. During the latter part of gestation, for example, the fetus is covered with a product of sebaceous secretion called the vernix caseosa which is both an electrical and a thermal insulator. Measurements of skin temperature overlying the vernix may be decreased due to its insulating capacity.[16] Recently, it has been proposed that the hydrophobic properties of the vernix play a potentially important role in diminishing heat loss due to evaporation following birth.[17]

3.4.3 Electrical Characteristics of the Thermistor

There are three properties required of a thermistor: linearity, interchangeability, and stability:

- **Linearity:** Thermistors typically exhibit very steep resistance-temperature profiles compared to other sensors. This rapid change in resistance in response to small variations in temperature allows the use of a simple driving circuit that corrects for any nonlinearity of the relationship curve between temperature and resistance over the measured temperature range.
- **Interchangeability:** Clinically, it is often necessary to replace thermistors rapidly in case of malfunctioning or for cleaning and sterilization purposes. Thermistors must be interchangeable with an error within the range of accuracy required for the measurement. An interchangeability tolerance of 0.2ºC or less within the physiological temperature range is acceptable for clinical practice.
- **Stability:** In addition to linearity and interchangeability, thermistors must be stable over time. Aging of thermistors results in a change in resistance-temperature characteristics over time which can be expressed as dR/dt. Resistance usually increases with time and is dependent on individual manufacturing processes. Typical stability values are about 0.01ºC over 100 days.[18]

Other factors to consider when designing or selecting a thermistor include the avoidance of self-heating of the thermistor element. Since a small current must be passed through the element in order to achieve resistance measurement, some ohmic heating will occur. The applied current, therefore, must be low enough not to artifactually increase thermistor temperature.

3.4.4 Probe Location

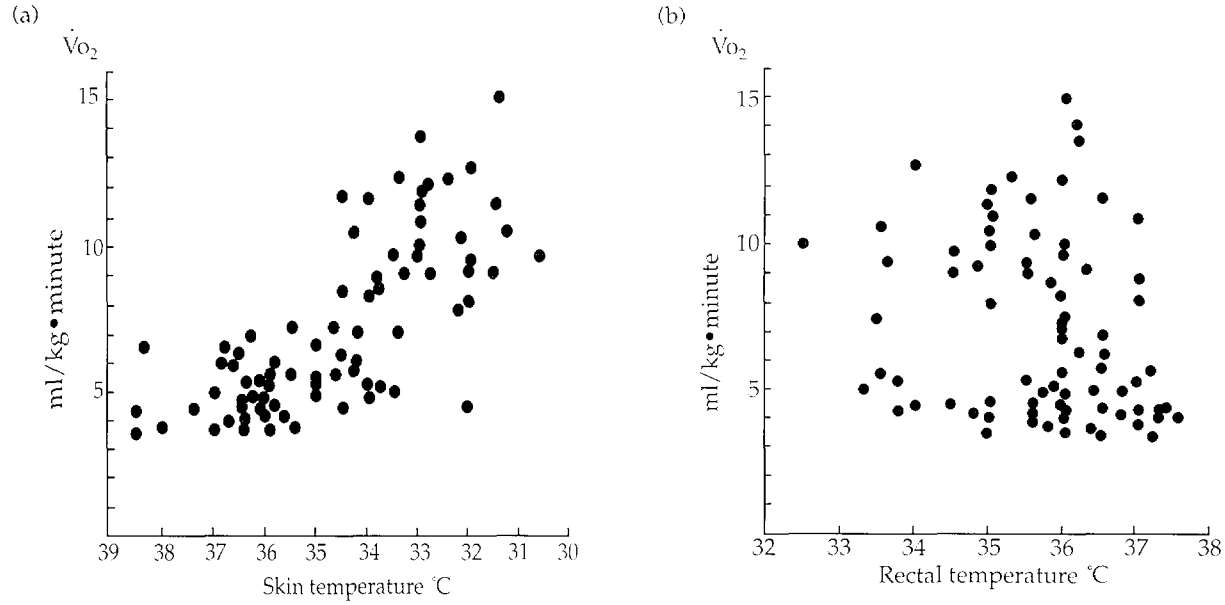
The surface of the body is in dynamic equilibrium with the environment. Visualization of the skin surface of newborn infants using noncontact methods (infrared telethermometry) demonstrates that skin temperature distributions are not uniform. Surface temperatures are frequently higher over the abdominal cavity (e.g., liver) and interscapular area (brown fat) and lower over the vasoreactive distal extremities. Consequently, placement of individual thermistors at distal sites (e.g., arms or legs) will result in lower temperature readings which may lead to increased heater output in servocontrolled incubators. Placement over bony structures may also lead to lower skin temperature readings and, thus, cause inadvertent overheating. Conversely, lo-

cation of thermistors over the brown fat area may result in higher measured skin temperatures with a secondary decrease in heater power output.

Various disease states may also change surface temperature distributions. In febrile patients, for example, cold feet are common, despite a high temperature at other body sites. This phenomenon reflects an increase in central temperature associated with peripheral vasoconstriction. In infants, the simultaneous measurement of skin temperatures over the abdomen and toe has been proposed as a diagnostic index of the temperature instability associated with sepsis.[19] A tummy-toe gradient greater than expected (approximately 2ºC) may indicate the presence of sepsis.[20] In contrast, external overheating due to incubator malfunction, for example, would result in peripheral vasodilatation and the equilibration of central and peripheral temperatures.

Finally, physiological temperatures may vary both laterally (along the skin surface) and vertically (from surface to core). In 1965, Adamsons and colleagues studied the relationship between systemic oxygen consumption and rectal, skin, and environmental temperatures in newborn infants subject to environmental cooling.[21] Their results indicated a direct relationship between metabolism and the gradient between the skin and the environment (see Figure 3.10a). Rectal (core) temperature was not predictive of metabolic rate in this study (Figure 3.10b). In the future, the judicious choice of location and insulation for surface probes[10] may allow noninvasive and continuous measurement of skin-core temperature gradients in order to determine appropriate thermal neutral zones for high-risk infants.

Figure 3.10 — (a) Oxygen consumption of newborn human infants as a function of the gradient between the body surface (skin) and environmental temperatures (Ts-E); (b) The relationship between oxygen consumption and deep body (rectal) temperature of newborn human infants under a variety of thermal environmental conditions. (from Adamsons K, Gandy GM, James LS. The influence of thermal factors upon oxygen consumption of the newborn infant. *J Pediatr.* 1965;66:498.)



3.5 Infant Warming Techniques

Most infants, especially those who are premature, arrive in the nursery in some degree of hypothermia. Physical intervention in terms of drying the skin surface, swaddling, or placement in a thermally controlled environment are required to maintain body temperature or initiate rewarming. The basic principles underlying infant warming techniques require an understanding of the mechanisms of heat loss described previously. An effort to minimize each of the components of heat loss will improve survival and ultimately reduce the need to divert calories from growth to unnecessary metabolic heat production.

At present, there are two primary, device-based methods for managing the thermal environment of low birth-weight infants in neonatal intensive care units.[22,23] The first, (and historically older), of these methods involves the servocontrol of forced air, convective incubators using either skin temperature or air temperature as the controlled variable (Figures 3.1 and 3.9). The second widely used method consists of infrared radiant warming,[23-25] a method that is generally servocontrolled to the skin temperature. Major differences exist between these different heating modes.

In convective incubators, increasing the relative humidity or swaddling the infant when appropriate results in a decrease in evaporative heat losses. Using double rather than single-walled incubators or adding plastic heat shields will decrease radiative heat losses. Handling the baby through specially designed portholes reduces convective heat losses, and using an incubator rubber foam mattress will decrease conductive heat transfer.[26]

Radiant warmers are typically used because of ease of handling and visualizing the infant compared to closed convective incubators. Unlike convective incubation (or the intrauterine state) this mode of heat delivery results in large differences in surface temperature between exposed and unexposed skin areas. Insensible water loss and, thus, evaporative heat losses are higher by 40% to 50% under radiant warmers than in convective incubators.[5,27] This may be due to a combination of factors including higher skin-air temperature gradients and a lower relative humidity in the nursery (macroclimate) than in the incubator (microclimate). In order to compensate for this increased water loss, an adjustment of the infant's total fluid intake should be made.

3.6 Servocontrol

Several modes of temperature control in infant incubators are used to regulate the heater power output.[28,29] Most modern incubators allow the caregiver to choose between skin temperature servocontrol, air temperature servocontrol, and manual (nonservo) control. With skin servocontrol, heater output automatically adjusts to changes in the temperature of the infant's skin thermistor. A change in the sensed temperature will result in a decrease or increase in heater output. Air temperature servocontrol acts the same as skin temperature servocontrol, but the controlling variable is the temperature of the air (or the incubator's wall in some cases). Manual control requires human intervention to maintain the desired temperature. A knob is changed in response to intermittent measurement of skin or air temperature. Manual control is seldom used in modern neonatology.

At present there is no clear answer to the question of which servocontrol mode is best. Skin servocontrol has the advantage of keeping the baby's skin temperature con-

stant at all times. Changes in humidity, air currents, or wall temperature will have a smaller effect on the baby's skin temperature when compared to constant heater output (manual control). Dislodgement of the probe or accidental placement of the thermistor between the body and the mattress may result in over or underheating of the baby, respectively. In addition, there may be large fluctuations in environmental and air temperature, which may have potentially untoward side effects (e.g., apnea).[30] Under skin temperature servocontrol, one also loses a major sign of disease (e.g., viz., fever). Air temperature servocontrol, on the other hand, will produce a more stable environment. In this mode of servocontrol, however, the patient is omitted from the thermal feedback loop.

In an effort to combine the benefits of both skin and air servocontrol, mixed servocontrol systems have been developed.[31] This mode of servocontrol uses skin temperature as well as air and incubator wall temperatures as input variables to a computerized algorithm which controls the heater output.[31] This system has the advantage of maintaining relatively stable environmental temperatures similar to an air servocontrolled incubator, but also incorporates the infant skin temperature as input to the feedback loop. Multiple input servocontrol systems are inherently more stable as major changes in one variable (e.g., detachment of the skin thermistor or accidental removal of the air probe) will result in a relatively small change in heater power output.

3.7 Summary

In mammals, birth marks a transition from a warm and wet environment to one that is cold and dry. Homeothermic mechanisms which have evolved to facilitate this transition include metabolic heat production by brown adipose tissue and the development of a hydrophobic skin surface to minimize evaporative heat loss. Newborns are assisted in this transition by caregivers who dry, swaddle, and temporarily place the infant within a controlled thermal environment. The prevention of cold stress, particularly in the vulnerable preterm or growth-retarded infant, is important to reduce morbidity and mortality. An understanding of the basic mechanisms of heat loss by conduction, convection, evaporation, and radiation facilitates the use of newborn thermal life support systems such as convective incubators and radiant warmers. The thermal environment maintained by these devices is usually controlled by servomechanisms to maintain a desired skin temperature, air temperature, or a combination of both. These temperatures are measured with thermistors in which a change in electrical resistance is related to a change in measured temperature. Close attention to the details of thermal management will facilitate the process of homeothermic adaptation in normal newborns and optimize the conditions for survival, growth, and early discharge in high-risk, growth-retarded, and preterm infants.

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4.0 PULSE OXIMETRY

Pulse oximetry technology was first developed as a research tool to noninvasively measure the effects of high-altitude and low-oxygen environments on World War II fighter pilots.[1] As pulse oximetry technology gained acceptance in the clinical setting, it soon became standard practice to monitor oxygen saturation during diagnostic testing (such as polysomnography), as well as during invasive surgical procedures.[2] More recently, pulse oximetry technology is being routinely incorporated into adult, pediatric, and neonatal, intensive care monitoring systems.[3]

As pulse oximetry has continued to gain acceptance in the neonatal and pediatric clinical settings, questions have arisen regarding its applicability and accuracy in this select population. For instance, does fetal hemoglobin, pulse rate, or ultraviolet lighting influence the pulse oximeter's accuracy? However, before addressing these and other issues, in this section, a brief overview of a pulse oximeter's operating principles is given.

4.1 Principles of Operation

Pulse oximetry combines techniques of light transmission and reception, spectrophotometry and photoplethysmography to noninvasively measure arterial oxygen saturation.[4,5] Spectrophotometry measures hemoglobin oxygen saturation, while photoplethysmography differentiates arterial from venous blood.

4.1.1 Spectrophotometry

Spectrophotometry can estimate hemoglobin oxygen saturation since the color and optical density of the hemoglobin molecule changes according to the amount of oxygen bound to it.[6] Oxygenated hemoglobin (HbO_2) is bright red, while deoxygenated hemoglobin (Hb) is dark blue; accordingly, each species of hemoglobin has its own light absorption characteristics.[6,7] The largest difference in absorption characteristics between HbO_2 and Hb is near the 660 nanometer (nm) range, which is the frequency of red light. When red light, with a frequency near 660 nm, is transmitted through well oxygenated blood, a significant amount of the light passes through the hemoglobin molecule. On the other hand, if the blood is deoxygenated, much less light is able to pass through the hemoglobin molecule. Therefore, the color of the hemoglobin molecule determines the amount of light which can pass through it, and the color of the molecule is primarily determined by the amount of oxygen bound to it.

In addition to red light, pulse oximetry uses a second light wavelength. This wavelength, between 800 nm and 1000 nm, is in the infrared region. In this region, oxygenated and deoxygenated hemoglobin absorbs about the same amount of infrared light.[8,9] Consequently, the transmission and reception of infrared light is relatively unaffected by the color of the hemoglobin molecule. Therefore, one purpose of the infrared light is to provide a constant value to which changes in transmitted and received red light intensity can be compared.

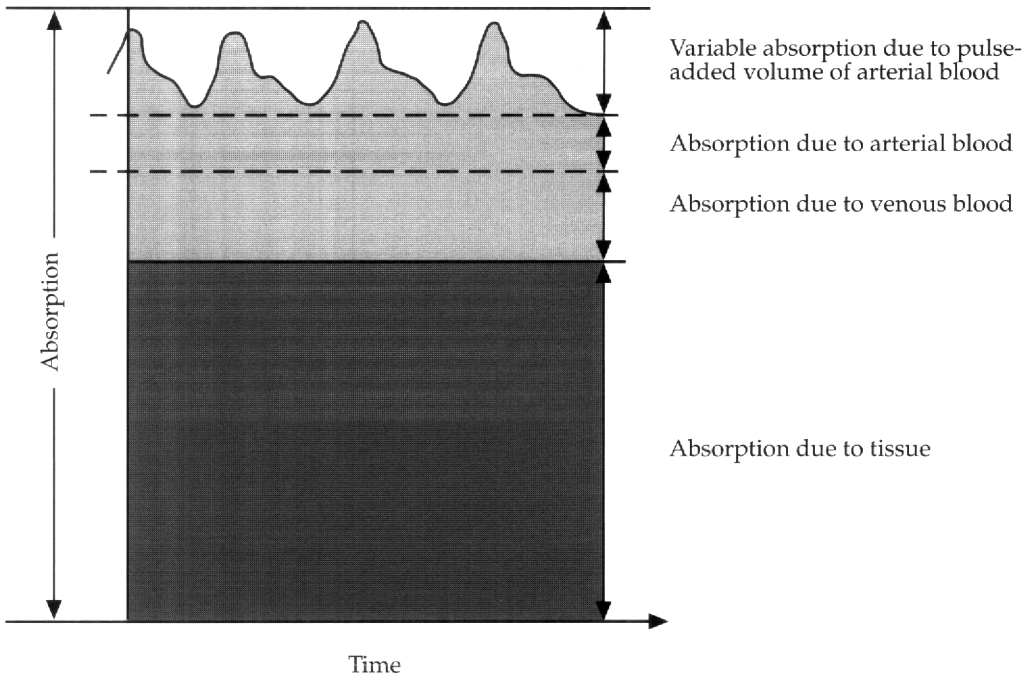
Red light transmission through blood is dependent upon hemoglobin oxygen saturation, but infrared light is not. Therefore, a ratio between the intensity of the received red and infrared light can be calculated. It is the ratio of red-to-infrared light that the oximeter uses to derive a value of oxygen saturation.

4.1.2 Photoplethysmography

Photoplethysmography uses light reflectance or light transmission through vascular tissue to measure arterial pressure waveforms generated by the cardiac cycle. In turn, noninvasive relative estimates of arterial blood flow, blood pressure, and tissue perfusion can be obtained. The basic principle of photoplethysmography is as follows: if a constant amount of light is transmitted through a pulsating vascular bed, more light is transmitted through the bed when the arterioles are nearly empty (cardiac diastole) than when the arterioles are mostly full (cardiac systole).[10]

The filling and emptying of the arterioles affect the path length of the transmitted light causing the received light's intensity to fluctuate. The fluctuating part of the received light's intensity is defined as the alternating current (AC) signal. As Figure 4.1 illustrates, there are other potential modifiers of the transmitted light, such as tissue or venous blood. However, since these substances absorb a constant amount of the transmitted light, their influence upon the transmission and reception of the light signal is essentially static. This static portion of the signal is called the direct current (DC) signal. By isolating the pulsatile, or AC, portion of the received light and spectrophotometrically measuring oxygen bound to hemoglobin during that time, estimates of arterial hemoglobin oxygen saturation can be obtained.

Figure 4.1 — Tissue composite shows dynamic and static components affecting light absorption. (from Wukitsch M. Analysis of Theory, Technology and Practice. *J Clin Mon.* 1988;4:293-294.)



4.2 Technical Considerations of Pulse Oximetry

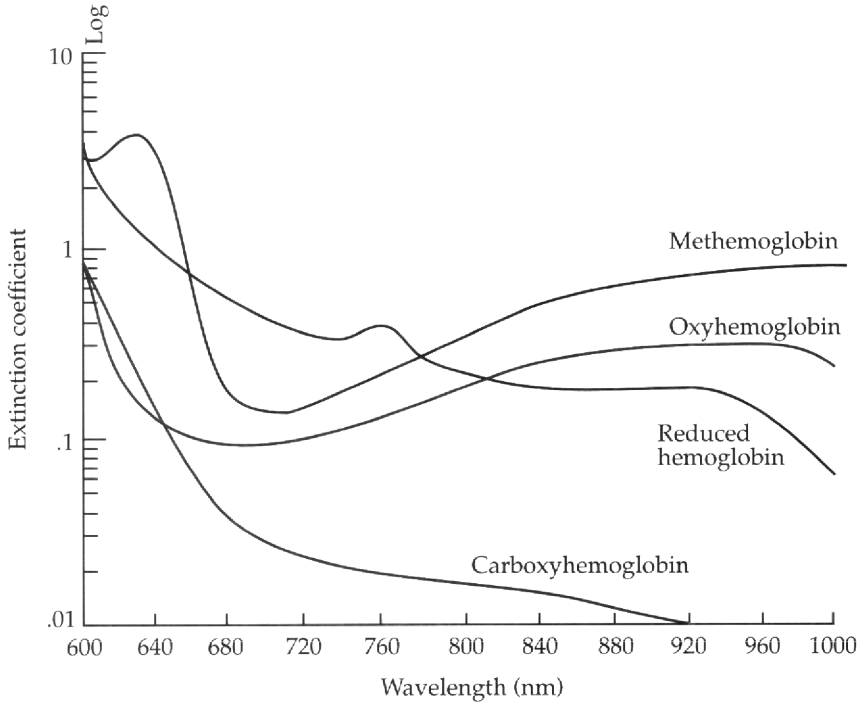
4.2.1 Dyshemoglobins

As previously described, pulse oximeters derive values of oxygen saturation by calculating the ratio of received red and infrared light. While the primary modifier of this red-to-infrared ratio is the color of the hemoglobin molecule, dyshemoglobins (of which methemoglobin and carboxyhemoglobin are examples) also modify the red-to-infrared ratios. In short, dyshemoglobins are forms of hemoglobin that do not bind oxygen, but do affect the color of the hemoglobin molecule.

Four distinct species of hemoglobin exist in the blood: reduced hemoglobin, oxyhemoglobin, methemoglobin, and carboxyhemoglobin. Consequently, four separate light wavelengths are required to differentiate one from the other. Once the percentage of each species of hemoglobin is measured, then the ratio of oxyhemoglobin to total hemoglobin can be calculated. The ratio of oxyhemoglobin to total hemoglobin is termed fractional oxygen saturation. Calculations of fractional oxygen saturation are obtained by co-oximeters, devices capable of *in vitro* measurements of oxygen saturation.

As Figure 4.2 illustrates, reduced hemoglobin and methemoglobin absorb similar amounts of red light with a wavelength near 660 nm. Also, carboxyhemoglobin and

Figure 4.2 — Extinction curves of reduced hemoglobin, oxyhemoglobin, methemoglobin, and carboxyhemoglobin. (from Wukitsch M. Analysis of Theory, Technology and Practice. *J Clin Mon.* 1988;4:293-294.)



oxyhemoglobin have almost identical absorption characteristics at 660 nm. Consequently, pulse oximeters which use a red light frequency near 660 nms cannot differentiate methemoglobin from reduced hemoglobin, nor can they differentiate oxyhemoglobin from carboxyhemoglobin.[11] Therefore, the value that pulse oximeters display as percent oxygen saturation is actually a sum of the four hemoglobin species and is termed functional saturation.

Fortunately, the percentage of carboxyhemoglobin and methemoglobin in neonates and the pediatric population is usually very small, and a presence in these trace amounts does not significantly alter the accuracy of pulse oximeters. However, there are conditions in which large amounts of dyshemoglobins are present and can affect the accuracy of pulse oximeters. They have been described in detail in this series entitled, *Respiration*.[12] However, the following synopsis provides clinically relevant examples of when pulse oximetric measurements of oxygen saturation should be validated by laboratory analysis of arterial blood gases.

The first example is carbon monoxide poisoning. In the presence of increased levels of carboxyhemoglobin, two-wavelength pulse oximetry cannot accurately estimate HbO_2. Therefore, in cases of smoke inhalation or suspected carbon monoxide poisoning, invasively drawn blood samples must be measured with co-oximetry to determine the percentages of oxyhemoglobin and carboxyhemoglobin[12] in the patient's blood.

The second clinical scenario in which an unusually large proportion of a dyshemoglobin exists is methemoglobinemia. As illustrated in Figure 4.2, in the light wavelength range near 660 nm, methemoglobin has absorption characteristics similar to reduced hemoglobin. Consequently, two-wavelength pulse oximetry cannot accurately estimate proportion of reduced hemoglobin within the blood. Therefore, in those clinical conditions in which excess methemoglobin exists, the oximeter may display falsely low values of oxygen saturation.[12]

Finally, radiographic dyes injected into a patient will also affect the accuracy of pulse oximeters. Since most radiographic dyes are either methyl blue or green, a prominent amount of blue dye in the arterial blood can be misinterpreted by the oximeter as being deoxygenated hemoglobin. These effects of intravascular dyes are transient, but unrecognized it may lead to erroneous clinical decision making.[12]

4.2.2 Anemia

In healthy, full-term newborns the hematocrit tends to rise in the first few days after birth to a value near 53 ± 5%; then between 2 and 4 months of age, it begins to fall to a value near 34 ± 3%. In the preterm infant, the fall in hematocrit is far more abrupt, with the minimum hematocrit appearing in 6 to 8 weeks.[13] Consequently, following birth a physiologic anemia occurs which may be compounded by co-existing pathological processes.

The theoretical basis of concern is that the oximeter algorithm expects the red light to be scattered by a predetermined amount of red blood cells in any given area. The oximeter can increase or decrease its light transmission intensity to compensate for light scattering as well as tissue thickness. However, in an anemic condition, the light may not be scattered to the same degree and more transmitted red light could reach the photodiode and potentially create a falsely high value of oxygen saturation. This effect has been shown in theoretical models but not yet duplicated in a clinical setting.[14]

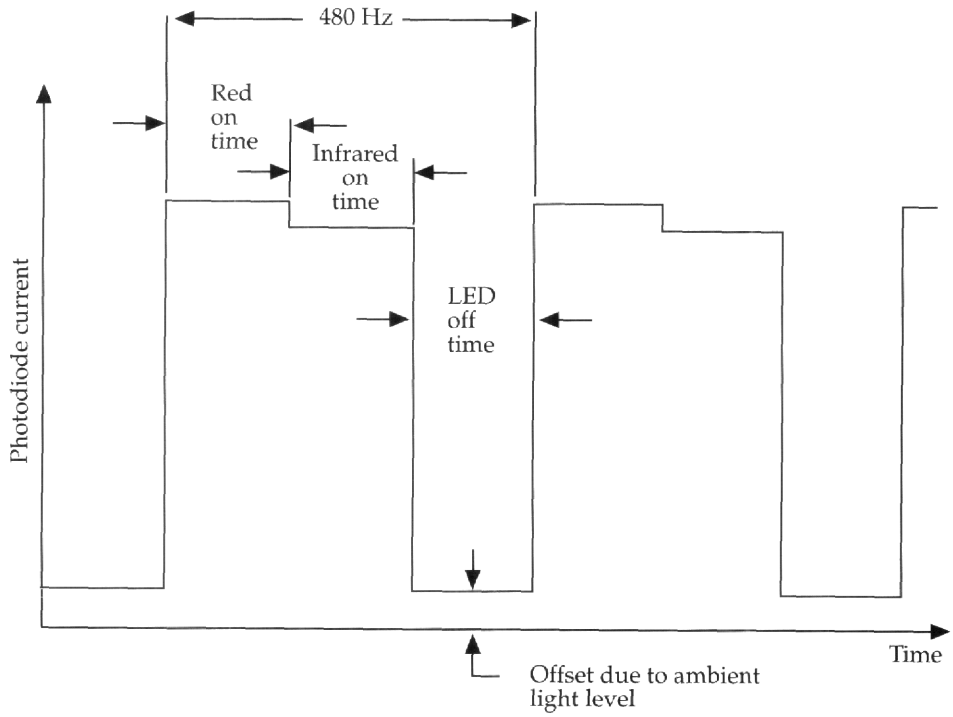
4.2.3 Skin Pigmentation

Dark skin pigmentation is associated with greater degrees of error in pulse oximetry measurements.[15,16] One plausible reason for this is that the melanin, found in the epidermis, absorbs a portion of the light transmitted by the pulse oximeter. This, in turn, causes a decrease in the signal-to-noise ratio. Consequently, the increase in the signal-to-noise ratio has the potential to cause erroneous values of oxygen saturation, or an error message from the pulse oximeter, to be displayed.

4.2.4 Ambient Light and External Light Sources

Pulse oximeter sensors have separate light emitting diodes (LEDs) to transmit red and infrared light. However, the sensor only has one photodetector. To measure each light independently, a pulse oximeter may first flash the red LED on and the photodetector measures its intensity after it has passed through the monitoring site. It then turns the red LED off. Next, the infrared LED is switched on, and the photodetector measures its intensity after it has passed through the monitoring site. The infrared LED is then switched off. Finally, both LEDs are off and the photodetector measures

Figure 4.3 — Illustration of red and infrared lights switching on and off to allow measurement of ambient light level.



the ambient light intensity.[17] The ambient light intensity is subtracted from the values of red and infrared light. This sequence, illustrated in Figure 4.3, occurs several hundred times per second.

Intense light from fluorescent lamps, operating room lights and infrared heat lamps have been reported to interfere with pulse oximeter performance.[18,19] External infrared light sources may increase the intensity of the infrared signal measured by the sensors photodetector. Consequently, this may lower both the displayed heart rate and oxygen saturation. These effects may appear erratically and may not be readily reproducible. Hence, decisions made on oximetry values should be consistent with clinical presentations.

4.2.5 Motion Artifact

When an oximeter sensor is on a monitoring site that is subjected to motion, the intermittent contact of the sensor with the skin can mechanically modulate the path length of the transmitted light. In turn, the ratios of red-to-infrared light are no longer modulated by the color of the hemoglobin molecule or by the pulsating vascular bed. Figure 4.4 graphically displays data collected from the analog outputs of a pulse oximeter. The oxygen saturation signal (top panel) and arterial pulse waveform signal

(middle panel) were collected and digitized at 50 Hz. Simultaneously, a three-lead electrocardiogram (bottom channel) was monitored and digitized at 50 Hz. The oxygen saturation signal is shown with a reduced resolution to illustrate signal stability; therefore, arrows are used to mark its corresponding times on each strip. These tracings emphasize that for each QRS complex seen and recorded on the ECG channel, a corresponding pulse waveform peak occurs within approximately 0.5 seconds. Since a peak-for-peak correlation between the pulse waveform and ECG channel exists, the value for oxygen saturation (derived from the pulse waveform) is representative of arterial blood.

Figure 4.4 — Pulse waveforms following within 0.5 seconds of each QRS complex supports values of oxygen saturation being plausible.

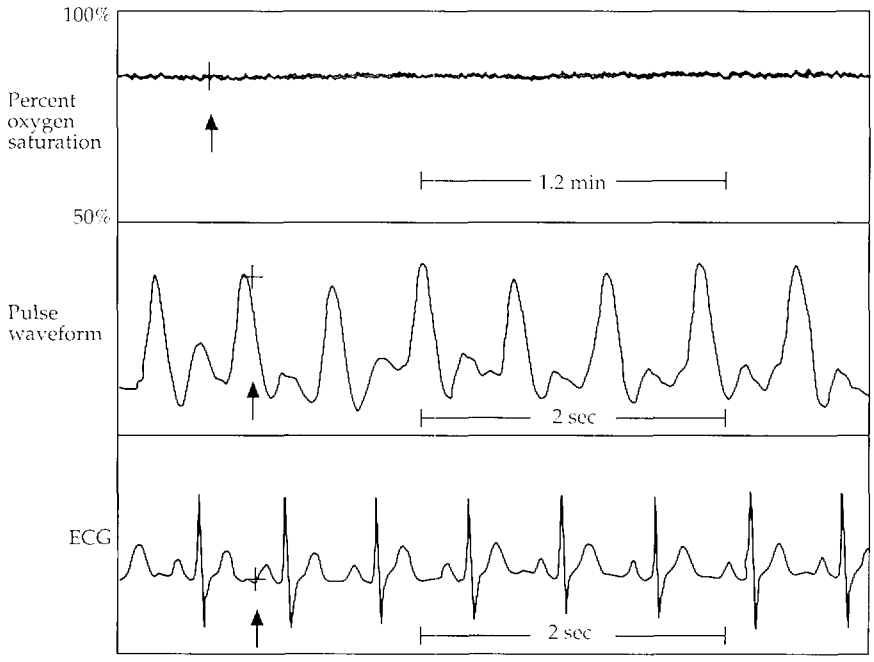
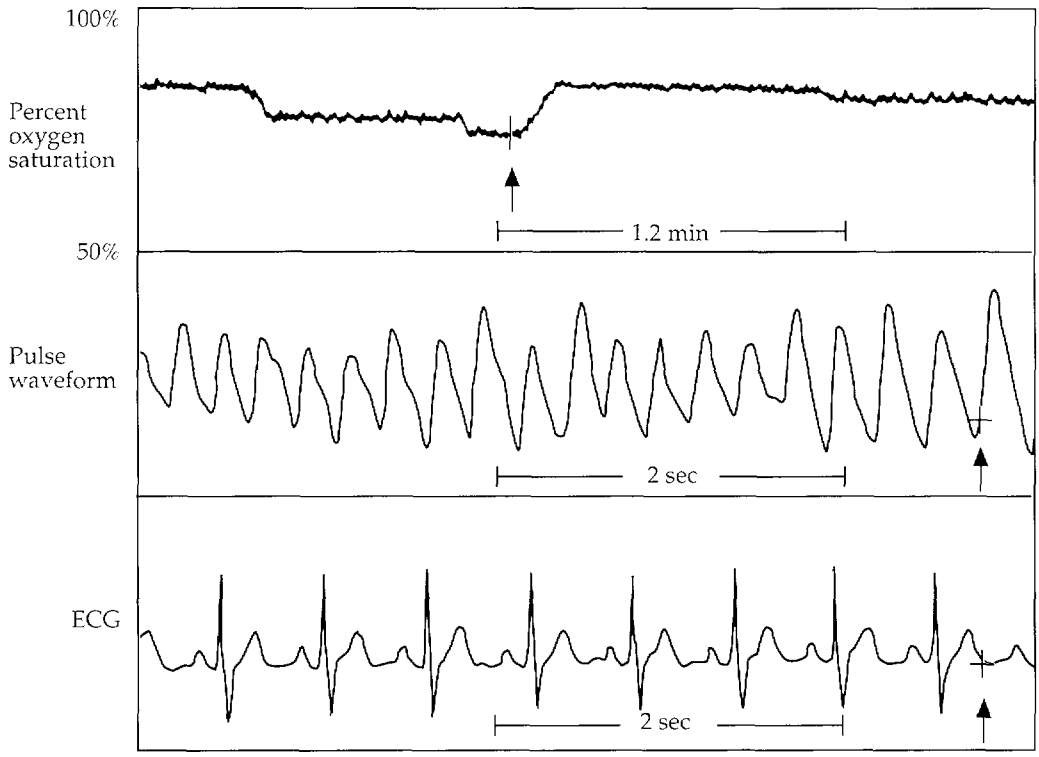


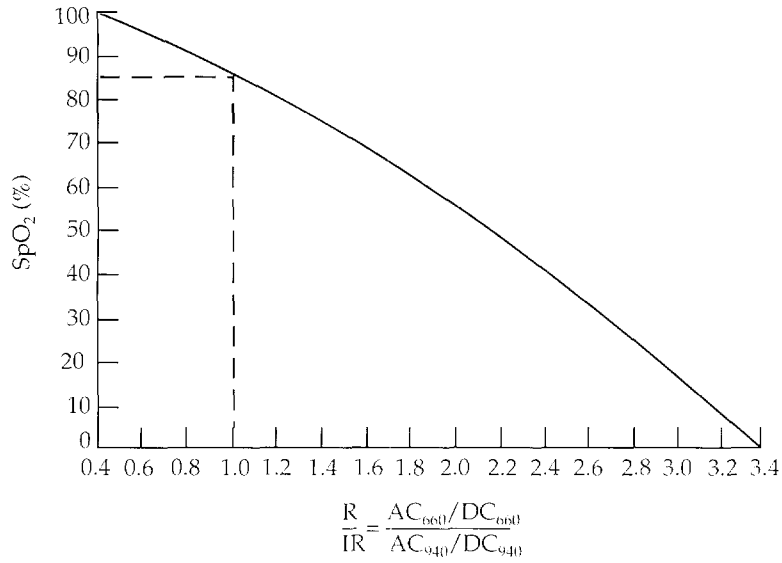
Figure 4.5 displays signals collected from the same subject using the same collection and display paradigm previously described. This tracing highlights the effects of motion upon the pulse waveform signal. Unlike Figure 4.4 in which clearly identified arterial pulse waveforms correspond with each QRS complex, this figure illustrates randomly occurring pulse waveforms. The frequency and amplitude of these artifactually induced waveforms may elude the oximeter's analog and digital filtering techniques. For example, in this illustration, the oximeter is providing a value of 87% oxygen saturation; however, the actual value of oxygen saturation was 96%.

Figure 4.5 — Pulse waveforms not corresponding with QRS complexes suggests erroneous values for oxygen saturation.



One possible explanation of why pulse oximeters can calculate values of oxygen saturation from artifactually induced changes in light intensity is that the artifactual pulse waveform may generate an AC signal larger in amplitude than the genuine arterial pulse-modulated AC signal.[17,20,21] Because of the artificially heightened pulse amplitude, the ratio of the red-to-infrared signals becomes almost entirely a function of a DC signal. Due to the large amplitude, the voltage of the two signals is similar and their ratio to each other becomes 1. The calibration curve in Figure 4.6 is representative of the curve that most pulse oximeters use to convert ratios of red-to-infrared light into a value of oxygen saturation. As can be seen, a red-to-infrared ratio of 1 is equal to an oxygen saturation of 84% to 88%. Unfortunately, since these values of oxygen saturation may appear to be clinically reasonable, their authenticity can only be verified by an inspection of the pulse waveform's integrity and its direct correlation with each heartbeat.

Figure 4.6 — Red-to-infrared ratios of 1 correspond to an oxygen saturation value between 84% to 88%. (from Wukitsch M. Analysis of Theory, Technology and Practice. *J Clin Mon.* 1988;4:293-294.)



In an attempt to overcome the affects of motion artifact, pulse oximetry technology uses a variety of artifact rejection schemes. One strategy is data averaging. This method averages several seconds worth of data and then displays the mean value observed during that period. Some oximeters employ predefined templates of arterial pulse waveforms to which all incoming pulse waveforms are fitted. Those waveforms which do not fit the template may be discarded. Another technique to filter out artifactual pulse waveforms is to use weighted pulse waveform averaging schemes. This strategy applies a weight or a measure to the quality of the incoming pulse waveform. Poor quality waveforms are then minimally weighted in the final calculation of oxygen saturation. These strategies are explained in detail in the volume in this series entitled, *Respiration.*[12]

4.3 Special Considerations for Neonatal Monitoring

4.3.1 Fetal Hemoglobin

Fetal hemoglobin is biochemically different than adult hemoglobin. The difference occurs in two of the four polypeptide chains of the globin moiety. Fetal hemoglobin is composed of two alpha and two gamma chains, while adult hemoglobin is composed of two alpha and two beta chains. The difference in fetal hemoglobin's polypeptide chains account for increased affinity for oxygen.[13]

Studies in the literature indicate that while fetal hemoglobin is biochemically different than adult hemoglobin, there are no perceptible differences between the absorption spectra of fetal hemoglobin and adult hemoglobin. *In vitro* studies by Mendelson[22] have compared the absorption spectra of fetal hemoglobin to adult hemoglobin and have found that between the wavelengths of 650 nm and 1000 nm (the range used by oximeters) there was no difference in light transmission and reception. *In vivo* studies by others,[23,24] support Mendelson's findings that large percentages of fetal hemoglobin did not affect the agreement between their pulse oximeter and measurements of oxygen saturation obtained by laboratory co-oximetry analysis of arterial blood samples.

4.3.2 Hyperbilirubinemia

Hyperbilirubinemia does not appear to affect the accuracy of current two-wavelength pulse oximeters. In a study performed by Chelluri et al.,[25] oxygen saturation values obtained with pulse oximetry were compared to those obtained from invasive measurements. Eighteen patients with normative values of bilirubin and 21 patients with bilirubins > 20 mg/dL were used as the study population. There was no appreciable difference between groups with respect to the mean bias and precision of pulse oximetry measurements to invasive measurements of oxygen saturation.

4.3.3 Hyperoxia

Hyperoxia should not be evaluated by pulse oximetry alone. Some studies suggest that if pulse oximetry values are maintained between 92% to 94% during administration of high oxygen gas concentrations, then acceptable values of PaO_2 are maintained.[26] However, these studies were done under controlled conditions which incorporated periodic blood gas measurements. Also, the study sample may not be generalizable to all neonatal or pediatric ICU patients.

The main reason to advocate against the use of pulse oximetry to monitor for hyperoxemia is based upon the shape of the oxyhemoglobin dissociation curve. In the region above 90% oxygen saturation, very large increases in PaO_2 can occur, yet only a 1% to 2% corresponding increase in oxygen saturation will follow. Therefore, there are risks that hyperoxemia could occur and not be reflected in the pulse oximeter's display of oxygen saturation.

4.4 *Pulse Oximeter Sensor Technology*

The typical pulse oximeter sensor configuration is one or two red LEDs and one infrared LED located on one side of the monitoring site. A photodetector is positioned on the opposite side of the monitoring site, directly opposing the LEDs. The function of the red and infrared LEDs are to transmit red and infrared light, while the photodetector measures their intensity on the opposite side of the monitoring site. These types of sensors where light is transmitted by LEDs and received by a photodetector are called transmittance sensors.

The primary consideration of transmittance type sensors is that the monitoring site should not be so thick as to prevent transmission of light through it. This often

limits sensor sites to either fingers, ears, or toes. However, in the neonatal and pediatric population, fingers and toes may be subject to frequent movement and sensor displacement.

Some manufacturers provide neonatal and pediatric sensors whose size is based upon the patient's weight. These sensors are designed to be attached to the patient with adhesive tape and are less likely to become dislodged than the clothes-pin type, spring-loaded sensors. Regardless of the sensor type, wrapping additional tape (other than that provided by the manufacturer) around the circumference of the oximeter sensor and the digit that it is attached to should be discouraged. The rationale is that if the digit and sensor are subjected to flexion or extension, then the adhesive tape tends to tighten and may impede circulation to the digit.

Although pulse oximetry measurements are predominantly considered to be risk-free, there have been reports of patients receiving burn injuries from pulse oximeter sensors.[27,28] Clinicians should take care to use only sensors that are recommended by the manufacturer as being compatible with the specified oximeter. Use of a sensor that is incompatible with the oximeter may result in overheating. Some pulse oximeters have a mechanism to protect against such incompatibility by sending a signal through the sensor to identify its circuitry.

4.5 Summary

All currently available pulse oximeters use LEDs to transmit red and infrared light through a vascular bed to a photodetector positioned opposite the LEDs. As the light passes through the vascular bed, its intensity is modulated by the filling and emptying of the arterioles. Both the red and the infrared lights are modulated by the pulsating arterioles. However, the red light is further modulated by the color of the hemoglobin; the darker the hemoglobin molecule, the more red light it absorbs. The photodetector positioned opposite the LEDs measures the intensity of the red and infrared light that have passed through the vascular bed. From this, the ratio of red-to-infrared light is used to determine arterial oxygen saturation.

When arterial oxygen is measured *in vivo* via pulse oximetry, the value produced is termed SpO_2. *In vitro* measurements of arterial oxygen saturation, obtained by arterial puncture and co-oximetric analysis of the sample, are termed SaO_2. Both pulse oximetry and co-oximetry use light transmission and reception to measure oxygen bound to the hemoglobin molecule. The distinction is that co-oximetry uses multiple light wavelengths to produce separate measurements of oxyhemoglobin as well as dyshemoglobins. Therefore, a value of SaO_2 produced by co-oximetry represents only oxygen bound to hemoglobin. On the other hand, pulse oximeters use only two light wavelengths and, therefore, cannot differentiate between oxyhemoglobin and dyshemoglobins. Consequently, they measure total hemoglobin saturation. Hence, SpO_2 is the sum of both oxyhemoglobin and dyshemoglobins.

While pulse oximeters can be adversely affected by specific environmental, physiological or technical conditions, their convenience, lack of patient discomfort, and overall accuracy often outweigh these limitations. These positive factors will further promote the use of such devices in clinical settings during the forthcoming years. Therefore, clinicians who are familiar with the operating principles and the technical limitations of pulse oximetry will be better equipped to use this technology to its fullest potential.

4.6 References

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5.0 TRANSCUTANEOUS GAS MONITORING

The introduction of transcutaneous gas monitoring (TCM) in the 1970s marked an evolutionary phase in the assessment of tissue oxygenation and ventilation in neonates. It went beyond the invasive intermittent blood sampling analysis that had become the standard during the previous two decades. The ability to noninvasively and continuously monitor the ventilatory and tissue oxygenation status of the patient provides the clinician with objective documentation of ongoing clinical features as opposed to random blood gas analysis dissociated from the general physiological state.

5.1 *Theory of Operation*

The transcutaneous electrode is the heart of transcutaneous gas monitoring technology and provides clinically useful information by performing four basic functions:

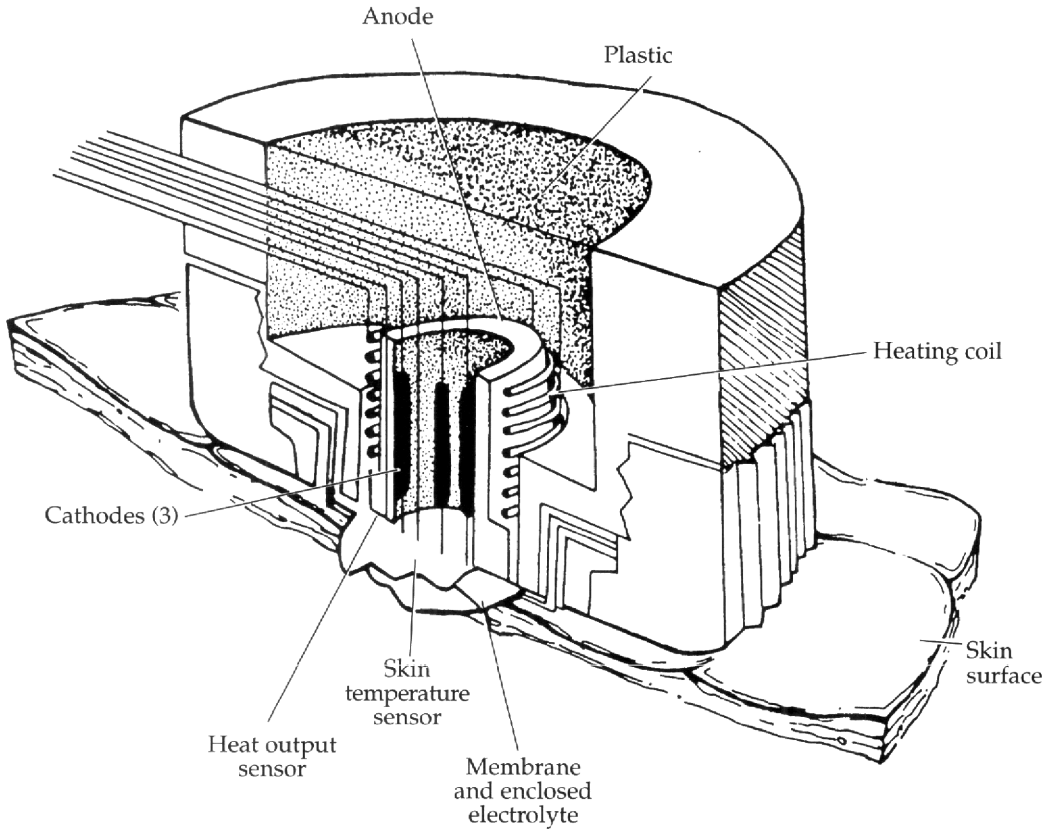
- Using a sensor to measure ionic current flow between silver-platinum electrodes in the presence of oxygen and then converting the electrical value to display partial pressure in mmHg on the monitor.
- Using a sensor to measure ionic current flow between a pH glass-silver/silver chloride wire in the presence of carbon dioxide which is displayed in mmHg on the monitor.
- Using a heater element and thermistor to provide a feedback system that allows the energy output to the sensor to vary so that it can maintain a constant temperature regardless of underlying flow.
- Displaying the quantitative energy output required to maintain constant sensor temperature. This energy output varies in proportion to the amount of capillary blood flow. Hence, it is an indicator of peripheral vascular perfusion to the area to which the sensor is attached.

5.1.1 Electrodes

Transcutaneous gas monitoring is the continuous measurement of oxygen and carbon dioxide partial pressures at the dermal surface utilizing electrodes that are specific to these gases. The oxygen electrode, or Clark electrode, and the carbon dioxide electrode, or Severinghaus electrode, are the same sensors used in laboratory blood gas analyzers.

The electrodes have been modified for transcutaneous applications. Technology has allowed the two electrodes to occupy one sensor housing which is an advantage when dealing with a neonate's limited body surface area, and the sensor is covered with a thin membrane which allows a gas-conducting electrolyte solution to be maintained between the electrode and skin. The sensor also contains a heater and thermistor which allow localized heating of the sensor site. The sensor is typically heated to 44ºC to enhance accuracy and response time of the monitor.

Figure 5.1 — Cross-section of TCM sensor. (from Levin DL, Morris PC, Moore GC. *A Practical Guide to Pediatric Care.* St. Louis, MO: C. V. Mosby Co.; 1984.)



The partial pressure oxygen (PO_2) electrode (Figure 5.1) is composed of a platinum cathode wire within a glass tube which is wrapped by a silver or silver/silver chloride anode. Another glass tube surrounds the structures and a potassium and phosphate buffer solution is injected, immersing the anode and cathode and serving as a bridge between the two. A polypropylene membrane seals the tip of the glass tube. When the oxygen permeates the membrane, an oxidation reduction reaction occurs between the anode and cathode:

$$O_2 + H_2O + 2e^- \rightarrow HO_2^- + OH$$

$$HO_2^- + H_2O + 2e^- \rightarrow 3OH^-$$

This electrochemical reaction is measured by a galvanometer and is displayed on the monitor. The CO_2 electrode is actually a pH electrode (modified) composed of a pH glass surrounded by a buffer and a silver/silver chloride wire, and is bubble-sealed within the glass. A silver/silver chloride band external to the glass serves as a reference electrode. The entire structure is immersed in a bicarbonate solution and enclosed within a glass tube with a Teflon membrane. Carbon dioxide permeates the membrane and is quickly hydrated causing a rise in the pH within the electrode. Therefore, a change in pH measured should solely be due to carbon dioxide once relative equilibrium is reached:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^- + HCO_3^-$$

This reaction is measured and displayed on the monitor.

5.1.2 Heating Element

Heating the electrode enhances accuracy for several reasons:

- Improved gas diffusion with a dilatation of the stratum corneum.
- A higher influx of arteriolar blood into the capillaries directly beneath the sensor.
- Reduced oxygen consumption of stratum corneum tissue at the sensor site.

Heating also causes an increase in tissue metabolism at the sensor site leading to a localized rise in CO_2. This phenomenon typically has low variability and can be compensated within the monitor. The sensor site must be changed within certain time intervals to prevent significant erythema and burning.

5.2 *Clinical Application*

The efficacy of transcutaneous monitoring is facilitated by the thin stratum corneum of the neonate. Similarly, adult and pediatric applications are feasible when values are interpreted appropriately in light of approximations for skin thickness. Grossman, et al., has demonstrated that gas diffusion resistance has a direct relationship to skin thickness. Therefore, as dermal cell proliferation develops in the newborn, adding to both the living and dead layers of the epidermis of the stratum corneum, a wider cor-

relation is expected. Despite the change in correlation, the information remains clinically useful.

In healthy neonates, studies indicate a close correlation (r = 0.97). For critically ill neonates on positive pressure ventilation, the correlation also remains statistically close (r = 0.94). Given this, any deviations in correlation can be attributable to physiologic changes in the patient as long as system integrity is maintained.

5.2.1 Site Selection

Placement of the sensor should be determined by evaluating the quality of the physical site itself and any physiological implications, e.g., venous admixture, altered perfusion, etc. Based on this, the following guidelines may be considered:

- The physical site should be an area with minimal bony prominences. Therefore, the lower chest would not be a preferred site.
- Gross pitting edema can also alter rate and amount of gas diffused. Edematous sites should be avoided.
- Areas with a large amount of fatty tissue should also be avoided. However, in neonates this finding would be rare.
- Finally, areas of the body that are cold may be hypoperfused and may not be accurate for reflecting central gas partial pressure. However, measurements will be accurate for oxygen delivered and CO_2 retained for that particular area.

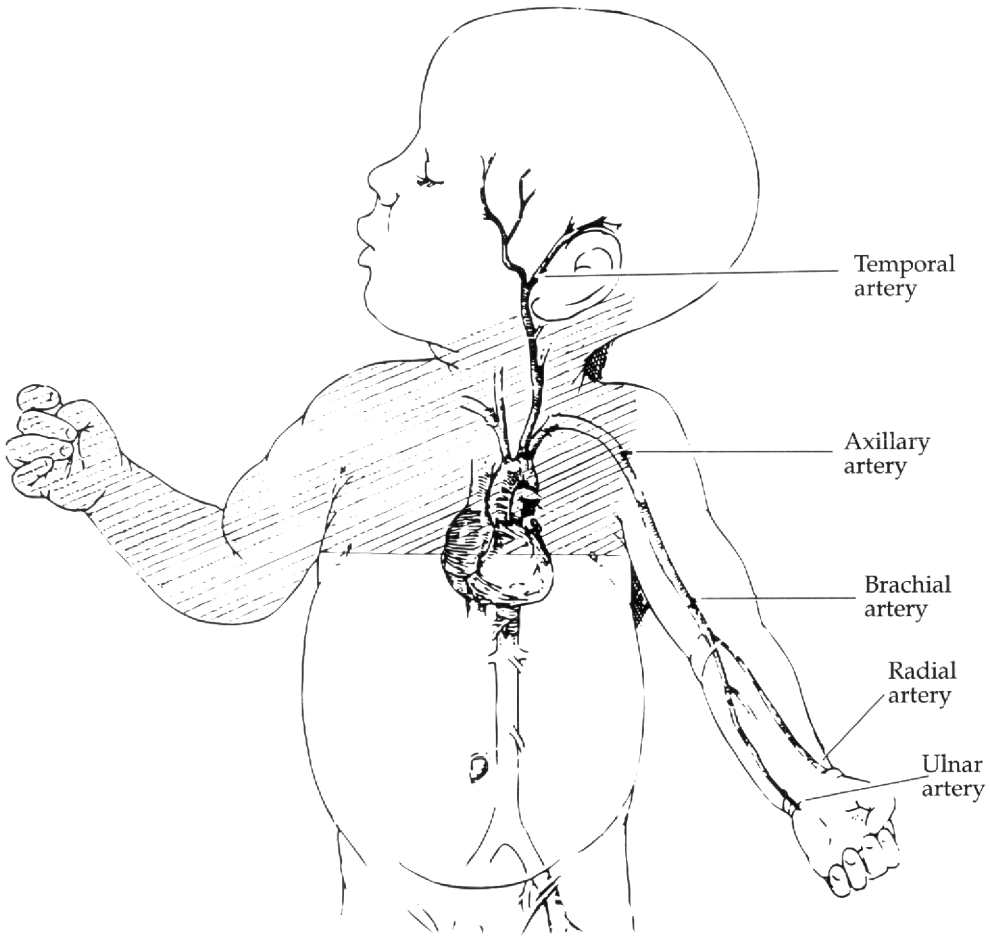
5.2.2 Preductal Versus Postductal Sites

The most common anatomical shunt in critically ill neonates occurs at the patent ductus arteriosus (PDA). In this case, the sensor should be placed in an area perfused prior to the PDA — typically the upper chest area from the nipple line and above (see Figure 5.2). The rationale for this is that there is a venous admixture of oxygenated blood in the aorta beyond the origin of the ductus with right-to-left shunting at the level of the PDA. Consequently, preductal blood to the eyes and the brain may have a higher PO_2. It has long been thought that excessive levels of arterial oxygen gas tensions in the blood (> 80 to 90 mmHg) may be a contributing factor to retinopathy prematurity in premature neonates. Additionally, abnormally high arterial oxygen tensions in the premature brain may cause changes in cerebral hemodynamics predisposing the neonate to cerebral insult. Placing the sensor in a body area after the PDA may lead to excessive administration of supplemental oxygen. Once the threat of anatomical shunts has been eliminated, the sensor can virtually be placed on any site that can accommodate its size.

5.2.3 Validation and Correlation

Although TCM does not eliminate blood gas sampling, it reduces the number of blood gases needed to assess the patient's oxygenation and ventilatory status. Blood gases should be drawn intermittently to develop a correlation with the values obtained by the TCM. During the first critical hours (48 hours to 72 hours) of the neonate, blood gases may need to be drawn as frequently as every 4 to 6 hours due to the

Figure 5.2 — Shaded area represents proper location of TCM sensor when there is a shunt at the patent ductus arteriosus. (from Merenstein GB, Gardner SL. *Handbook of Neonatal Intensive Care*. St. Louis, MO: C. V. Mosby; 1985.)



dynamic physiologic environment and immaturity or disease. After 72 hours, with resolution of disease entities and established stability, blood gas can be drawn less frequent (i.e., every 6 to 8 hours). The correlation should be more consistent as the patient enters the convalescent stage.

Good correlation is when TCM readings vary directly with arterial values. Typically, correlation is closer between transcutaneous PO_2 ($PtcO_2$) and arterial PO_2 (PaO_2) when oxygen tensions are within the normal range. The correlation should be re-evaluated if $PtcO_2$ is less than 30 mmHg or greater than 150 mmHg.

Many clinicians have discounted the reliability of TCM. However, there is often a sound physiological or application-related cause for the variation. To avoid application-related discrepancies adhere to the following guidelines:

- Apply sensor to the skin surface using direct pressure to avoid air bubbles under the sensor.
- Maintain sensor temperature at 43ºC to 44ºC.
- Select sites that are void of bony prominences, excussive edema and fat.
- Prepare the site by removing oils, dermal, and other debris, etc.
- Follow manufacturer's recommended proper calibration techniques.
- If required, polish the electrode membranes to remove oxidation residue.
- Periodically draw a blood gas sample as this remains the gold standard for assessing a patient's oxygenation and acid-base status.

Adequate tissue perfusion at the sensor site is essential to maximize correlation between $PtcO_2$ and PaO_2 values. Tissue perfusion is dependent on such variables as:

- Body temperature.
- Vasoactive medications.
- Site location.
- Blood pH.
- Cardiac output.
- Conditions affecting peripheral vascular resistance, such as sepsis.

Finally, the anatomic influence on a PDA with right-to-left shunting of pulmonary arterial blood should direct the clinician to place the sensor on the chest, above the nipple line, to enable accurate monitoring of oxygen delivery to the retina and brain. This is discussed in a later section.

5.2.4 Monitoring

Transcutaneous monitoring provides continuous real-time measurement of oxygen and carbon dioxide. This allows the clinician to dynamically intervene when indicated. By minimizing duration and degree of insults, patient outcomes should be improved.

These interventions are based on objective data as opposed to the more subjective methods of the past such as visualizing cyanosis, color of the blood, etc. The monitor can be set with alarm limits alerting the clinician to potential harm to the patient.

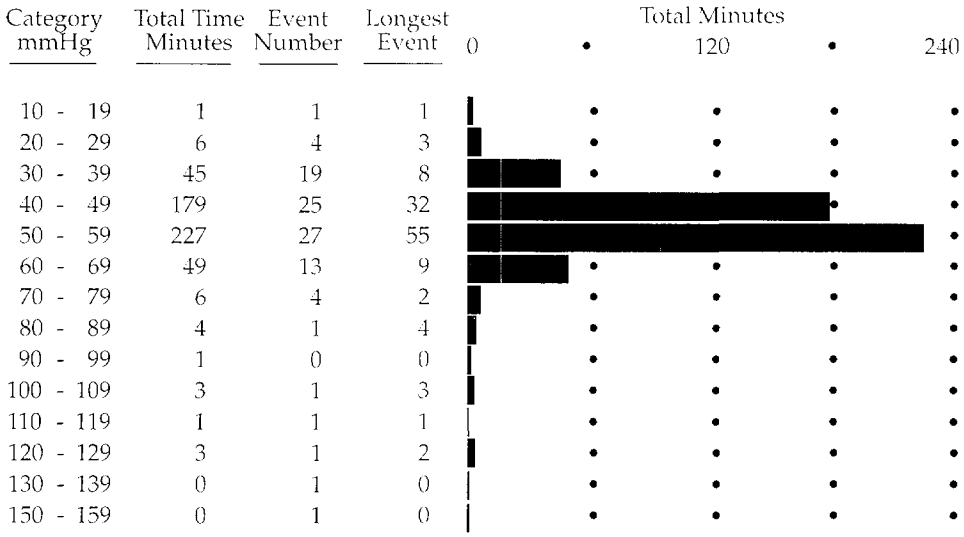
The heater element function may also assist in determining peripheral perfusion. With the sensor temperature set at 44ºC, the patient's own blood temperature will cool the sensor. This cooling will cause the monitor to increase its power output (in milliwatts) to the sensor heater in an attempt to maintain a temperature of 44ºC. Thus, the higher the perfusion to the sensor, the higher the power output to the sensor. The correlation of this in milliwatts can be displayed by the monitor and is usually labeled "local power" or "relative power."

5.2.5 Diagnostics and Quality Assessment

One of the most valuable applications for TCM is its use as a diagnostic tool. Unfortunately, this is probably the least used application. Printed copies of $PtcO_2$ and $PtcCO_2$ measurements provide valuable data to diagnose problems, determine timeliness of intervention, and assess efficacy of therapy that may cause changes in oxygenation and ventilatory status. The sequence of changes in relation to heart rate, blood pressure, and apnea/periodic breathing are easily demonstrated. The use of event markers documents precise timing of incidents that are of clinical significance. Analysis of these trends is very useful in quality improvement programs in clinical practice.

In addition to printed trend data, most applications include histograms indicating the percentage of time the patient's $PtcO_2$ and $PtcCO_2$ has been within certain set ranges (see Figure 5.3). This data can be collated to assess the effectiveness of care. As an example, wide scatter on the histogram would suggest agitation, lack of sedation, or ramifications from establishing minimal handling protocols to patient-triggered ventilation system. This is well demonstrated in the following example where the variability of $PtcO_2$ and $PtcCO_2$ are decreased by the institution of patient-triggered assisted ventilation using impedance technology.

Figure 5.3 — TCM histograms.



As mentioned earlier, TCM can be used effectively in demonstrating right-to-left shunting of blood leading to a venous admixture of blood at different anatomical sites. In the case of such a shunt at the level of the ductus arteriosus, the sensor is usually placed on a preductal site. If the patient has an umbilical artery catheter (UAC) *in situ*, the $PtcO_2$ can be compared with the central PaO_2 via the UAC, with due consideration of ductal shunting. Typically, a gradient greater than 20 mmHg is indicative of a right-to-left shunt. The wider the disparity, the higher the venous admixture. A

second sensor can be placed at a postductal site and $PtcO_2$ readings can be compared to assess the gradient between the two values. This technique enables the clinician to document efficacy of pharmacological and ventilatory interventions. In combination with the monitor relative power output values, the effect of such intervention on cardiac output may also be trended. Despite the inability to precisely quantitate cardiac output or tissue perfusion, such trends are useful adjuncts to document and assess efficacy of cardiopulmonary support to sick infants. They are invaluable in objectively enhancing continuous quality improvement programs in intensive care settings.

5.3 References

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6.0 APNEA

Apnea is defined as a cessation of breathing. It is a serious problem encountered in neonatology, especially in preterm infants, but it can also be seen in older infants (apnea of infancy). Some investigators hypothesize that this latter form of apnea is responsible for sudden infant death (SIDS), although this hypothesis has never been verified.

Apnea can present in infants in three different ways. Central apnea refers to a situation where infants stop breathing due to a lack of any central nervous system drive. In this case breathing effort as well as ventilation ceases. In the case of obstructive apnea, the breathing effort is present, but there is no ventilation of the lungs due to blockage of the airway. When both of these types of apneas occur together, it is known as mixed apnea. An infant may start by exhibiting central apnea and then, in an effort to reestablish breathing, go through the motions but not ventilate the lungs for the first few breaths due to an obstruction.

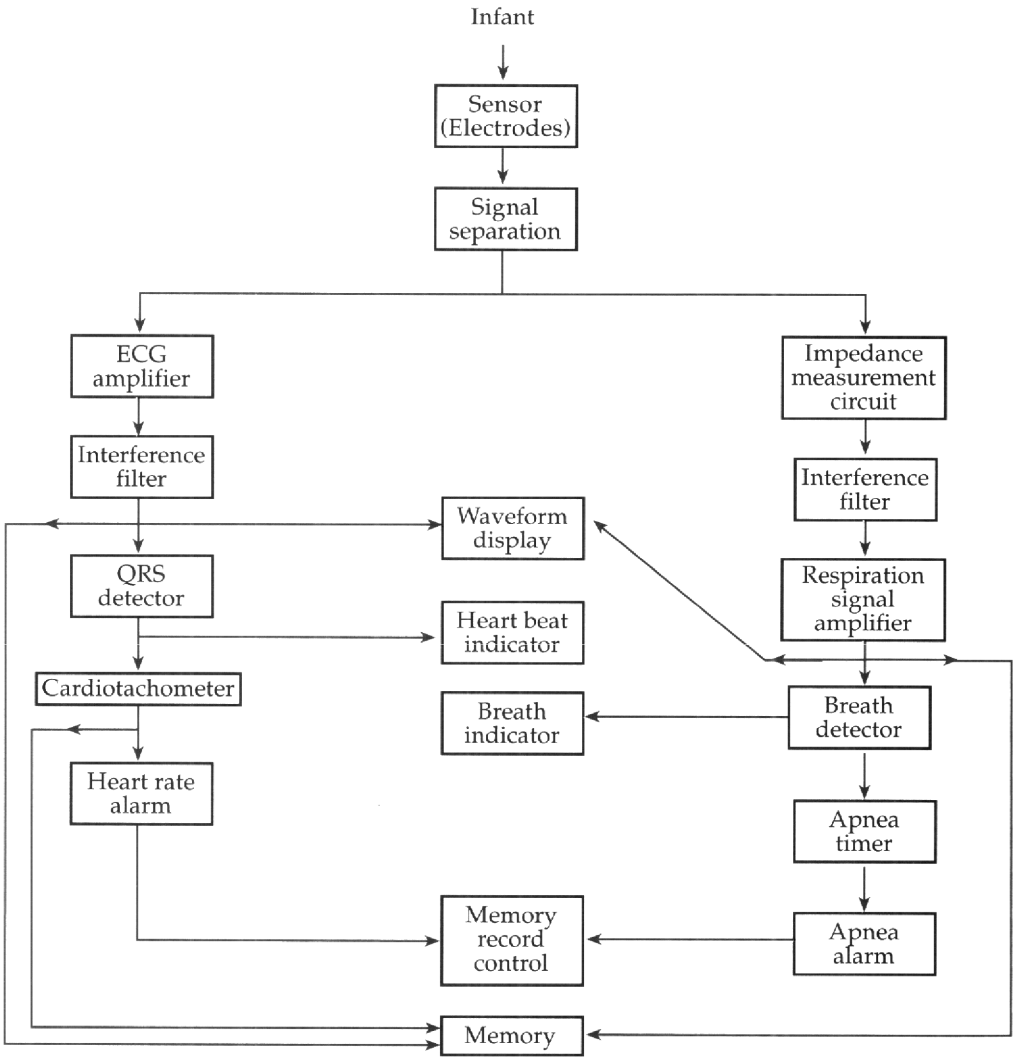
Prolonged apnea can be a serious problem that can lead to irreversible central nervous system damage and death; thus, it must be detected quickly and resuscitative measures instituted to avoid these problems. The development of electronic monitors to detect apnea has helped to make this possible.

Apnea monitors continuously observe respiratory activity and recognizes apnea when it occurs. The duration of the apnea is measured, and if it exceeds a predetermined limit an alarm alerts the caregiver to start appropriate resuscitative efforts. Although apnea monitors were originally developed for use in the hospital in neonatal intensive care units (NICUs), simplified versions have evolved that are used in the home setting.

An infant apnea monitor can be a rather complicated piece of electronic technology with internal computers and memory. Nevertheless, the basic functions of an apnea monitor can be reduced to: (1) sensing and patient interface, (2) signal processing, and (3) information storage and display.

Figure 6.1 illustrates the architecture of an infant apnea monitor showing the components of the monitor concerned with sensing breathing and detecting apnea. The sensor portion of the monitor provides the interface between the patient and the electronic system, and generates an electrical signal that is related in some way to the patient's breathing. The shape of this signal as a function of time represents the breathing pattern of the patient. The next section of the monitor carries out signal processing functions. It consists of many blocks which are used to prepare the signal so that breaths and apnea can be recognized and dealt with appropriately. The final portion of the monitor is concerned with the display and storage of pertinent data collected by the instrument. This display can be comprehensive in the case of monitors used in the NICU or very elementary in home monitors. In the following paragraphs, sections of the apnea monitor are discussed in more detail.

Figure 6.1 — Block diagram of the major components of an infant apnea monitor.



6.1 Sensing Respiration for Monitoring

The function of the sensor portion of the apnea monitor is to collect a signal related to breathing and convert it into an electrical quantity that varies with time according to the infant's breathing pattern. This signal represents the patient's breathing and can be processed by the rest of the monitor's electronic circuit. The sensor serves as an interface between the biologic system, the infant, and the electronic system of the monitor. Therefore, when considering sensors, it is necessary to contemplate biologic, clinical, and electronic concerns. There are many different types of direct and indirect sensors that can be used to carry out the sensing function.[1] Direct sensors are able to measure breathing by contacting the actual gas that is inhaled or exhaled, while in indirect sensors, sensor measurements are made of some secondary variable that is related to the process of inhalation or exhalation. An example of such a variable would

be abdominal wall movement; this is secondary to movement of the diaphragm which, in turn, results in the ventilation of the lungs.

Table 6.1 lists some of the more common direct and indirect methods of sensing respiration. Of these, the measurement of transthoracic impedance is by far the most frequently used for infant respiration and apnea monitoring. The direct methods can only be used if there is a direct connection to the airway (such as when the infant is intubated) and are, therefore, not practical for other uses. Indirect methods, on the other hand, can be used more conveniently because they do not require connection to the airway and can make their measurement using sensors attached to the chest or abdomen.

Table 6.1 — Direct and Indirect Methods of Sensing Breathing.

Direct Methods
1. Pneumotachograph
2. Spirometry
3. Airway carbon dioxide sensor
4. Airway temperature sensor
5. Anemometry
6. Air flow sound sensor
Indirect Methods
1. Transthoracic electrical impedance
2. Contacting motion sensors
a. Compliant strain gauge
b. Air-filled capsule
c. Displacement magnetometer
d. Inductance respirometry
3. Noncontacting motion sensors
a. Motion-sensing pad
b. Radiation reflection
c. Variable capacitance
4. Electromyography
5. Breath sounds
6. Intraesophageal pressure
7. Whole-body plethysmograph

The basic principle of transthoracic impedance measurement involves determining the ease with which a small electrical current can be passed through the chest.[2,3] Electrical impedance is a property of materials and electrical devices that describes how much electrical current (the flow of electrical charge) can be expected when a voltage (an electrical driving force) is applied to that material or device. Something with a low electrical impedance makes it easy for the electrical current to exist, while it is difficult for electrical charge to flow through materials or devices with high elec-

trical impedance. Thus, an electrical conductor such as a metal wire has a very low impedance, while an electrical insulator such as a piece of glass has a very high impedance. The electrical impedance of biologic tissue falls within a range between these two extremes, and is often more like a conductor than an insulator.

Electrical impedance covers a range of different types of voltage excitation of a material or a device. In the special case where this excitation is a direct current such as from a battery, electrical impedance reduces to the familiar concept of electrical resistance. However, when the applied voltage is a time-varying sinusoid over a range of frequencies, we must add an additional component, known as the reactance, to the resistance to describe the overall electrical impedance. Since infant apnea monitors measure impedance using a high-frequency sinusoidal voltage, both resistance and reactance must be considered in order to correctly understand the way the monitor functions. Fortunately, most biologic tissue has a fairly uniform reactive component of impedance, so that monitor function can be understood by looking only at the resistive component.

Many factors affect the impedance, or for the sake of argument, resistance, of an object. Figure 6.2 is a simplified example of a rectangular block of a uniform material. If electrical connections are made to this material on opposing sides and a battery of known voltage is connected through a meter that measures electrical current to this object, a complete electrical circuit is created. The amount of current that flows in this circuit will be determined by the battery voltage and the resistance of that particular object. This resistance, R, can be calculated using the formula:

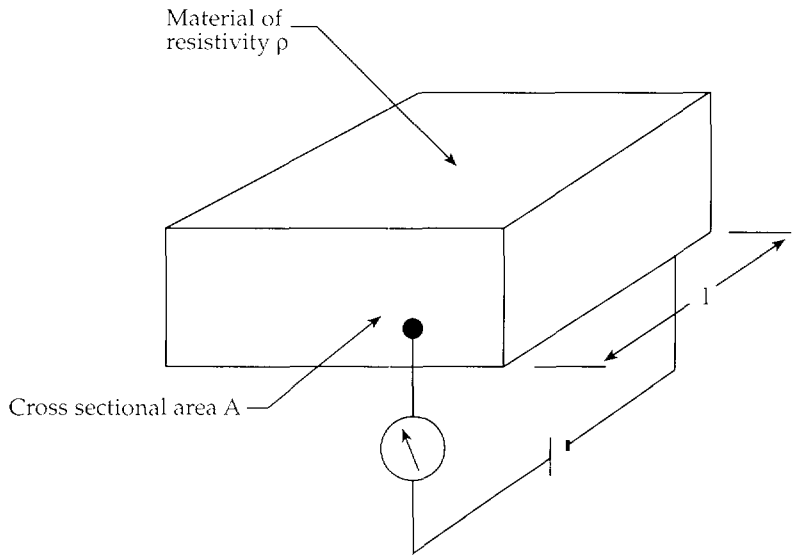
$$R = \rho \frac{l}{A}$$

where ρ = resistivity of the material
l = length of the object between the two electrical connections on opposite sides
A = cross sectional area of the object transverse to the axis connecting the two electrical contacts.

It can be seen from this equation that an increase in the object's resistivity or the distance between the electrical connections will increase the resistance while an increase in the cross-sectional area of the object decreases it. Thus, resistance is affected by (1) the electrical properties of the material being investigated and (2) the geometry of the measurement system.

Imagine that the uniform block of material shown in Figure 6.2 is replaced with the chest of a patient and consider the measurement of resistance as that patient breathes. Clearly, there are changes in geometry as the rib cage moves during breathing and as the result of changes in volume of thoracic structures, such as the heart and lungs, during a breath or heartbeat. There are also changes in electrical resistivity. First consider only the lungs. During exhalation, the alveoli are at minimal volume, and so the fraction of the lung volume that is made up of tissue and fluid will be much greater than at maximum inspiration when the alveoli are filled with air. Since air is a relatively poor electrical conductor (it has a very high electrical resistance or impedance) and parenchymal tissue is a relatively good conductor, if the object in Figure 6.2 is replaced with a segment of lung, there would be large changes in resistance from inspiration to exhalation.

Figure 6.2 — Measurement of the resistance of a rectangular slab of a uniform material.



Direct electrical access to the lungs is not possible for practical clinical monitoring, and electrodes can only be placed on the skin of the thorax. This results in a situation similar to what is seen in the thoracic cross-section of Figure 6.3. The impedance seen between these electrodes consists of contributions from many different types of tissue. The volume of some of these tissues changes with the cardiac and respiratory cycles, and these changes will result in changes in the impedance seen between the electrodes because of the changes in geometry. As the volumes of these tissues change, their contribution to the overall impedance will also change. This results in a change in effective resistivity as well as geometry. As the lungs fill with air, the amount of high-resistivity tissue increases. As the heart or vasculature fill with blood, there is an increase in low-resistivity tissue. Thus, as far as the chest electrodes are concerned, the impedance changes are from both geometric and resistivity effects.

Unfortunately, those tissues that result in the impedance changes with breathing and the heartbeat are surrounded by tissues that are relatively good conductors of electric current and tend to allow current to bypass the lungs as illustrated in Figure 6.3. The impedances associated with these tissues are relatively constant unless the infant moves, and then they can change as well due to geometric effects associated with the movement. Because the majority of the current passes through these superficial tissues, these changes can be much more substantial than those changes seen at the electrodes from the lungs, and this produces motion artifact which can be a major problem for transthoracic impedance monitoring. Figure 6.4 shows an example of a transthoracic impedance recording showing motion artifact as well as breaths, and how the artifact can obliterate the breathing signal.

Figure 6.3 — Cross section of the chest of an infant showing the pathway of current from a pair of electrodes on the chest surface connected to a transthoracic impedance apnea monitor.

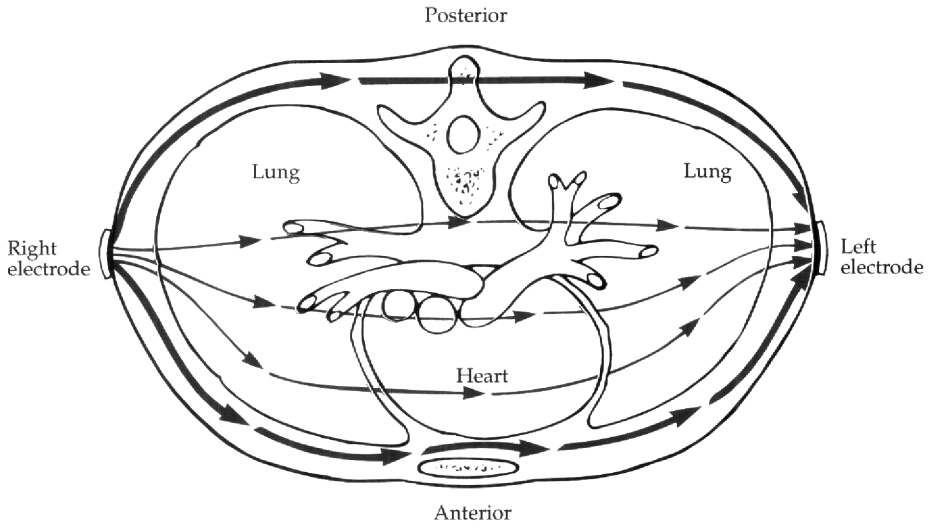
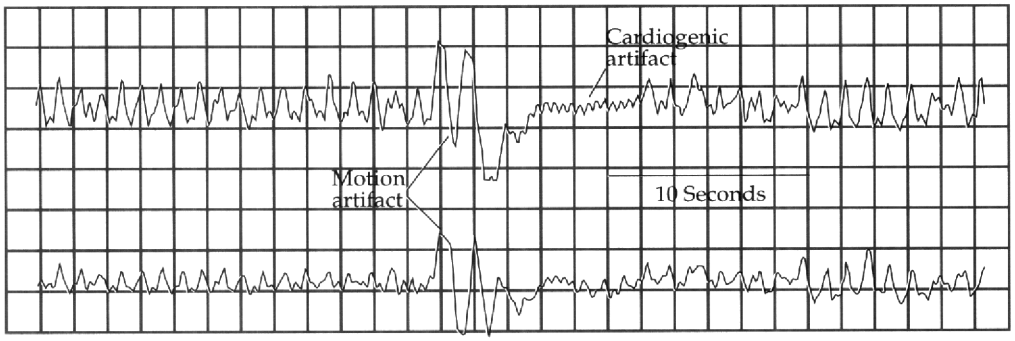


Figure 6.4 — Common artifact seen with transthoracic impedance apnea monitoring.



Changes in blood volume in the heart and vasculature over the cardiac cycle can also affect transthoracic impedance. Usually only small variations are seen with each heartbeat, but occasionally this cardiogenic artifact can be as great as the breath amplitude. Cardiogenic artifact, which is usually seen during periods of apnea, is shown in Figure 6.11a.

In a typical transthoracic impedance measurement in infants, the baseline impedance between the electrodes is generally about 500 ohms, and the variation due to breathing is usually no more than 0.5% of that, or 2.5 ohms.[4] On the other hand, variations due to motion can be of the order of tens of ohms; thus movement can completely obliterate impedance changes due to breathing. This is one of the major limitations of transthoracic impedance apnea monitoring.

6.2 Electrodes

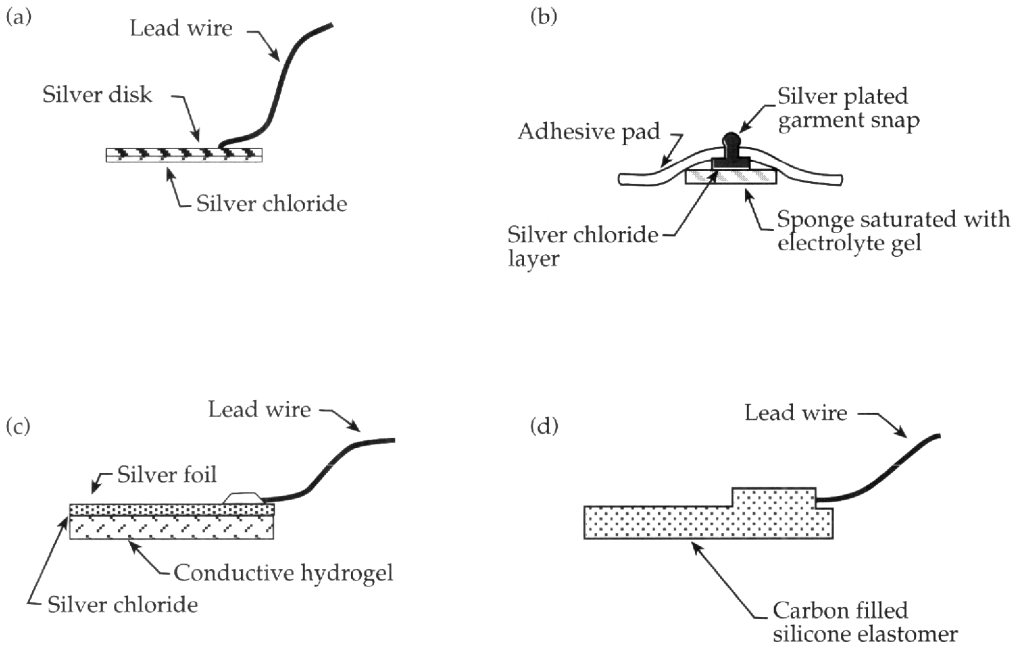
Electrical contact to the thoracic skin surface to measure transthoracic impedance is made by electrodes.[5] There are various forms of electrodes, and different types are optimal for different clinical situations. The most common form of electrode is shown in Figure 6.5a. The actual electrical connection is made by a small silver or silver-plated disk that is coated with a layer of silver chloride. A lead wire connects this disk to the apnea monitor. If the silver disk itself is placed on the skin, the electrical connection is not always reliable. Therefore, to improve the connection, an electrolyte gel is used. It consists of an aqueous base with dissolved salts such as potassium chloride or sodium chloride to make it conductive because of the dissociated ions. This gel wets the surface of the electrode and the surface of the skin to provide a reliable contact. A silver chloride layer is often grown on the surface of the silver disk to further enhance the interface between the silver electrode and the electrolytic gel. This helps to stabilize the electrode electrochemically and results in lower noise and artifact for the apnea monitor.

Although using a silver disk, the gel, and tape to hold the disk in place is one of the ways that electrodes were originally applied, more convenient forms have developed. In one of these (available as a disposable electrode), the electrolyte gel is held within an open-celled foam sponge that is glued to the surface of the silver disk. This type of electrode, illustrated in Figure 6.5b, is readily available as a commercial product. The electrodes are packaged with the gel already applied to the sponge so they can be easily applied to the infant. Often the electrical contact to the disk is carried out by a snap similar to a clothing snap. The male side of the snap is attached to the electrode disk with the female portion on the electrode lead wire.

A variation on this form of electrode is shown in Figure 6.5c. The sponge saturated with electrolyte gel is replaced by a layer of a conductive hydrogel. Hydrogel is similar in consistency to soft rubber and has a very sticky surface. This electrode has the advantage that the hydrogel serves both as the electrolytic gel and the adhesive, so hydrogel type electrodes can be smaller than electrodes that use a sponge. They also have the advantage of minimizing artifact due to a reduction in the relative motion between the electrode and the skin.

A fourth type of electrode used for home infant apnea monitors is illustrated in Figure 6.5d. This electrode, fabricated from a conductive silicone elastomer, is a piece of rubber that is filled with graphite powder to give it a black color. It can be used without any electrolyte. When the electrode is placed on the infant's skin, it blocks the evaporation of sweat from the skin surface. A thin layer of sweat forms after the electrode has been in place for a few minutes and, since the sweat contains sodium chloride, this serves as the electrolyte. Some users of these electrodes accelerate the formation of the sweat layer by putting a drop of saline solution under the electrode when they place it on the skin. These electrodes are usually larger than the sponge or the hydrogel electrodes, but they are soft and flexible and they conform to the shape of the skin surface.

Figure 6.5 — Skin surface electrodes used with infant apnea monitors: (a) simple silver/silver chloride disk electrode; (b) disposable electrode with electrolyte gel in an open-celled foam sponge; (c) hydrogel electrode; (d) carbon-filled silicone elastomer electrode.



There is an impedance associated with the interface between the electrodes and the skin which is generally different for the different types of electrodes described above. The conventional wet electrodes, shown in Figures 6.4a and 6.4b, have the lowest impedance, while the hydrogel electrode has the highest. These impedances vary as the electrodes are moved, and this variation further adds to motion artifact seen with transthoracic impedance measurement. Investigators have found that the electrode-skin impedance is smallest when the current passing between the electrode and skin is an alternating current (AC) at a frequency greater than 20 kHz.[6] Thus, virtually all apnea monitors operate at frequencies in the range of 30 kHz to 100 kHz, which minimizes motion artifact that is associated with the electrode-skin impedance. It also has the advantage that the body's sensitivity to shocks from high-frequency currents is much lower than for low-frequency current. Even though the current passed between electrodes in apnea monitors is so small as to not produce a shock hazard at any frequency, the use of high-frequency current makes this excitation doubly safe.

The lead wires that connect the electrodes to the monitor itself also have an impedance associated with them, and it can vary as these lead wires are moved. Thus, as far as the impedance measurement circuitry of the monitor is concerned, impedance variations are observed from multiple sources such as (1) breathing, (2) heartbeat, (3) tissue impedance changes with movement, (4) electrode impedance changes with movement, and (5) lead wire impedance changes with movement. The monitor cannot tell which of these sources is responsible for the impedance change it observes. Thus, a major problem is for the monitor to be able to detect those impedance changes that result from breathing and reject all others. At the present time no monitor has been able to completely meet this objective.

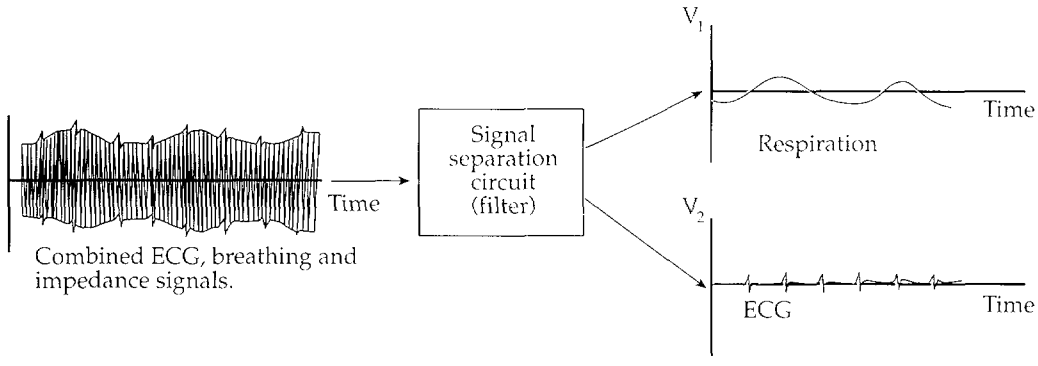
6.3 *Signal Processing*

The function of the signal processing section of a monitor is to extract information from the data being monitored and use that information to make decisions such as sounding an alarm. Signal processing covers a wide range of procedures. Some of those that are important for use in infant apnea monitors are briefly described in the following sections.

6.3.1 Separate Electrocardiogram and Respiration Signals

Most infant apnea monitors use the same electrodes to measure the transthoracic electrical impedance and the electrocardiogram (ECG) since they are also cardiac monitors. In this way, one set of sensors can be used for two functions. The problem this produces, however, is to be able to separate these two signals in the monitor. Since the frequencies of the transthoracic impedance signal at the electrodes and the ECG are quite different, this separation can be carried out by filters (illustrated in Figure 6.6).

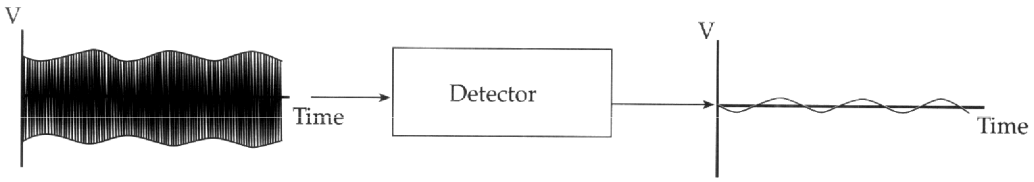
Figure 6.6 — Signal processing: separating ECG and respiration signals.



6.3.2 Extract Impedance Variations from Total Impedance

As discussed in the previous section, the variation of the transthoracic impedance due to breathing is quite small when one considers the overall impedance signal. It is unnecessary to process the baseline impedance since the breathing information is only in the variations. A circuit known as a detector can be used to extract the impedance variation from the total impedance signal so that only the variations are processed in the remainder of the monitor. This is illustrated in Figure 6.7.

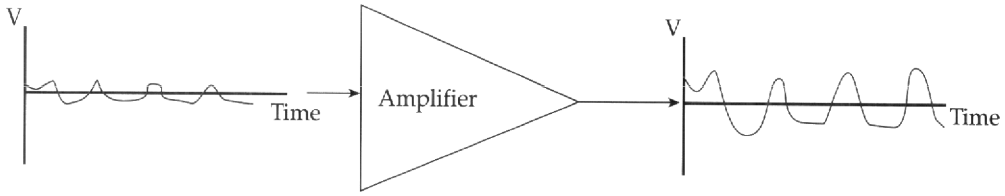
Figure 6.7 — Signal processing: separating the variation of impedance from the total impedance seen by a transthoracic impedance apnea monitor.



6.3.3 Amplify

Often the impedance variation (and the ECG) are very low amplitude and need to be increased in strength before it is possible to do additional processing. One of the most common signal processors is the amplifier, which takes a relatively weak signal at its input and produces a much stronger signal at the output as illustrated in Figure 6.8.

Figure 6.8 — Signal processing: amplification.

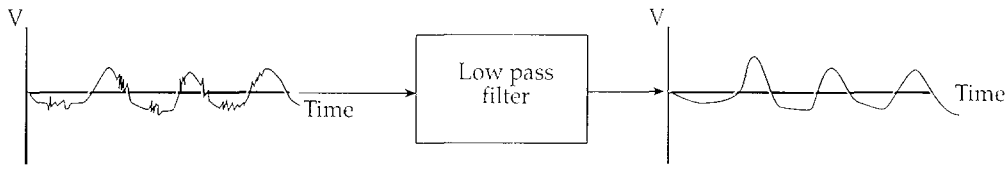


6.3.4 Filter

The mathematical analysis of signals such as those monitored by an apnea monitor shows that all signals are made up of a range of sinusoidal frequency components. It is possible to take a complex signal such as the ECG and break it down into a series of continuous sinusoidal waves having different amplitudes, frequencies, and phase. Signal bandwidth is the total range of frequencies of these components of a signal. Different biological signals (and noise or artifact) encompass different ranges of frequencies or bandwidths. A filter circuit can be used to select one range of frequencies

and reject all others. Thus, as illustrated in Figure 6.9, if a breathing signal has some noise covering a different frequency band contaminating it, a filter can be used to eliminate the noise and allow only the signal to pass. Filters can be used to separate two different signals that are passed along the same channel such as the impedance and ECG signals illustrated in Figure 6.6. When the frequency band of two signals or a signal and noise overlap, however, there is no filter that can completely separate the signal or eliminate the noise.

Figure 6.9 — Signal processing: filtering.

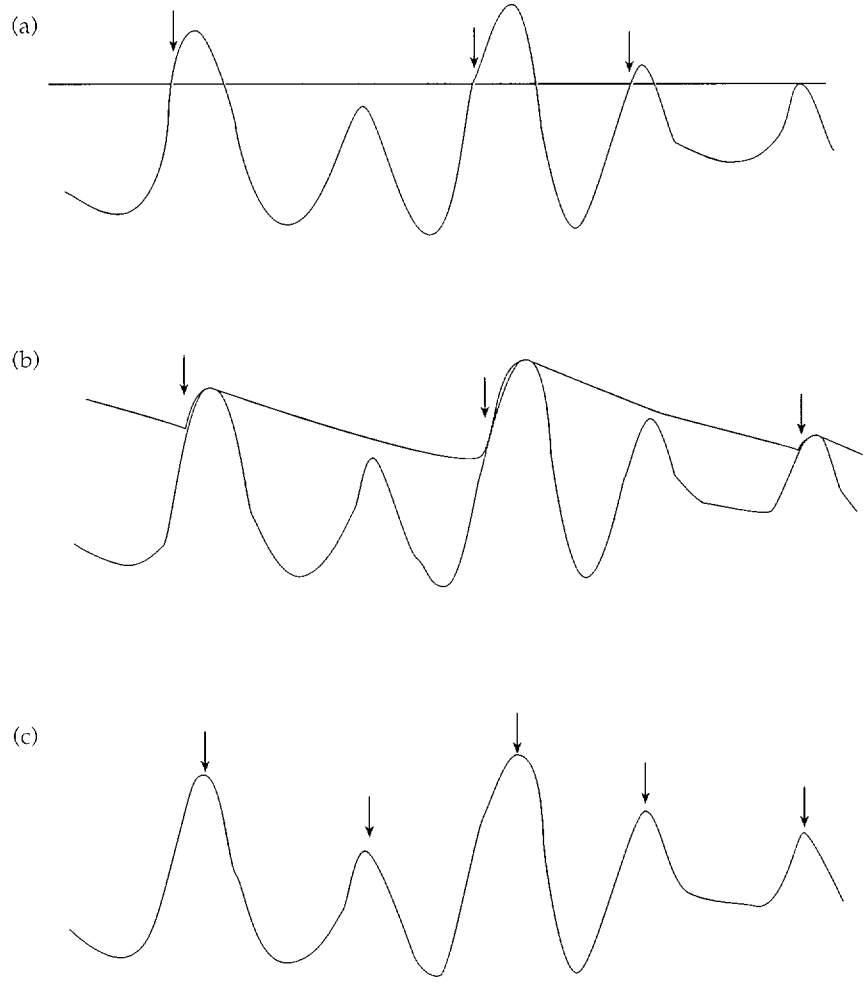


6.3.5 Breath Detection

One of the most important signal processing functions of an apnea monitor is the identification of each breath in the signal. By detecting a breath the monitor knows that apnea is not present. Figure 6.10 illustrates three of the commonly used breath detection schemes for apnea monitors. In threshold detection, a breath is identified every time the signal goes above a preset threshold. When breathing amplitude is regular and greater than the threshold, this method can work quite well and it has the added advantage of being very simple to implement. A problem arises when breath amplitude is not regular, which is often the case with infants. Under these circumstances, small breaths can be missed as illustrated in Figure 6.10a. One way to get around this problem is to use a variable threshold rather than the fixed threshold. In this way the threshold level is set by the amplitude of the previous breath or of a group of previous breaths. In sophisticated adaptive threshold detection schemes, the threshold itself is variable and decreases with time so that if a breath is missed because its amplitude was beneath the threshold, the next breath at that amplitude will be detected. This is illustrated in Figure 6.10b. One runs the risk with such a system that if there is, in fact, apnea, eventually the threshold will become low enough that noise on the baseline will trigger the breath detector and deceive the monitor into thinking a breath is occurring. Thus, when adoptive thresholds of this type are used in monitors, there needs to be a minimum level for the threshold that is higher than the noise amplitude.

Peak detection is a third method of breath detection that is used in apnea monitors. As illustrated in Figure 6.10c, this method detects the peak of any breath waveform no matter what its amplitude might be. This method can be quite reliable, however, when there is noise or cardiogenic artifact on the breathing signal, there can be extra peaks of the signal due to this noise. In this case, these will be detected as breaths, and the monitor will be detecting more breaths than are occurring.

Figure 6.10 — Signal processing: detection of breaths: (a) fixed threshold; (b) adaptive threshold; and (c) peak detection.



A method of breath detection that has not received widespread application in commercially available monitors, but offers many advantages over those described above is based on pattern recognition. Instead of just looking at something as simple as a peak or the crossing of a threshold, a computer is used to analyze the breathing signal and to look for breaths in much the way that a clinician would while reading a recording from the monitor. Features of the breath signal such as amplitude, duration, rate, and wave shape are determined; and each suspected breath on the breathing signal is analyzed from the standpoint of all of these features. The computer asks whether each particular feature is within the physiologic range for the type of patient being monitored, and if all of the features meet that criteria, the suspected breath is identified as an actual breath. If these conditions are not met, the suspected breath is rejected.

6.3.6 Removal of Cardiogenic Artifact

Another aspect of signal processing in an infant apnea monitor is the application of several approaches to reducing or removing cardiogenic artifact in the respiration waveform. Although filtering is the simplest approach for doing this, it is not entirely effective since the frequency components of the cardiogenic artifact and the respiration signals overlap. Some monitors use adaptive filtering wherein the monitor determines the cutoff frequency for the filter based on the heart rate, but this can still create problems when the heart rate and breathing rate are close to one another, something that can occur in small infants. The primary problem caused by cardiogenic artifact is that this inadvertently may be recognized as a breath during periods of apnea. This is a serious problem for it can cause the monitor to fail to alarm during a prolonged apnea. A signal processing approach that is used to avoid this problem without removing the cardiogenic artifact from the signal is to look for simultaneous breath and heartbeat detection on the respiration and heart rate channels of the monitor. This is another reason why cardiac monitors are combined with apnea monitors. If several heartbeats and breaths coincide, a coincidence-detection circuit can be used to disregard the associated breaths since they could be due to incorrect detection of cardiogenic artifact. Thus, the monitor would still be able to detect the apnea. The risk of this processing approach is that, in the rare case where the heart rate and respiration rate are the same, an apnea could be detected even though it did not occur.

6.3.7 Measurement of Apnea Duration

Once the signal processor of an apnea monitor detects the absence of breathing, it can measure the duration of time over which no breaths are seen. If the time from the last breath exceeds a preset limit, the signal processor will activate an alarm.

6.3.8 Memory Management

Many of the more recently developed hospital and home infant apnea monitors have memories for storage of waveforms, events detected by the monitor, and, in the case of home monitors, compliance in the use of the monitor. Signal processing in these monitors can be quite complex because it must determine which signals or event classifications are to be stored in memory and then place them in the appropriate portion of the memory. It is also important for the signal processor to monitor the memory to determine when it is getting close to being completely filled so that the operator can be alerted to correct the situation and, thus, avoid losing important information due to memory overflow.

Memory management also involves getting information out of memory and back to the monitor displays, which involves being able to read the appropriate part of the memory where the information is stored.

6.3.9 Problems in Signal Processing

Although the signal processing steps described previously appear to be straightforward and able to make apnea monitoring very reliable, this, unfortunately, is not the case. Indeed, if the infant's breathing signal was regular, as shown in the example of Figure 6.11a, it would be possible to have reliable breath and apnea detection. However, the signal can also have a configuration like that shown in Figure 6.11b; in this case, it is very difficult to carry out reliable processing. In addition to irregular breathing, there are the problems of motion artifact and cardiogenic artifact. Although some of the signal processing techniques described above can reduce the effect of these problems, there is no foolproof method of eliminating the artifact or the interference to breath detection caused by the artifact.

6.4 *Storage and Display*

The function of this final portion of an apnea monitor is to store data for later interpretation and to show current or stored data on an appropriate display, such as a computer screen.

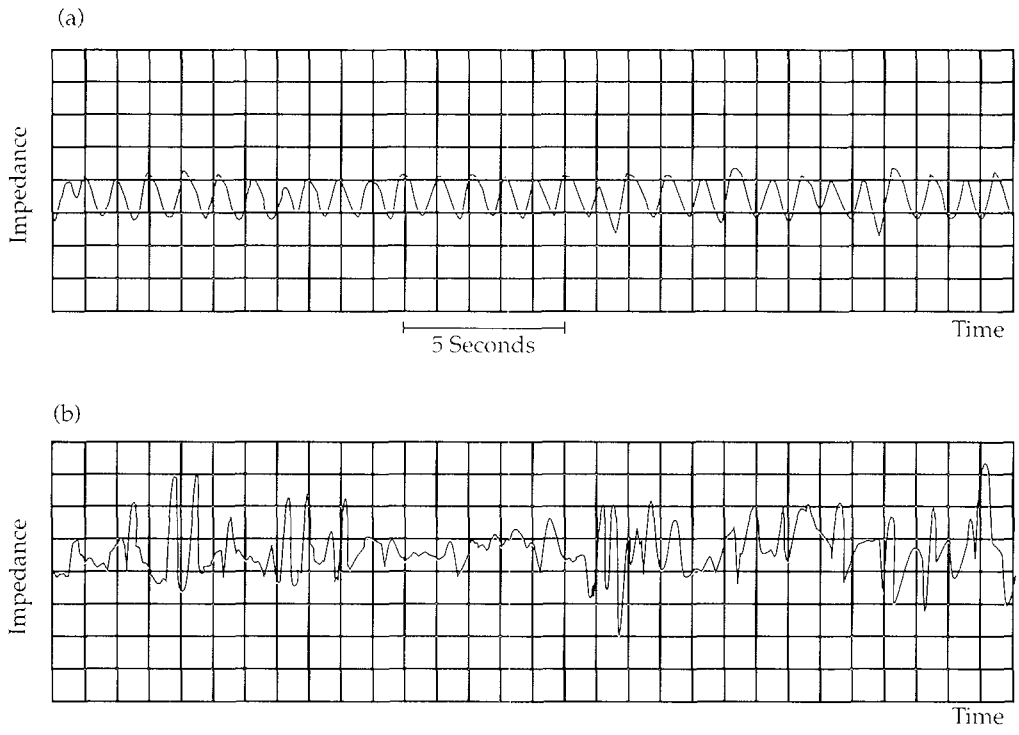
6.4.1 Storage

Monitored information considered relevant is stored in memory in the monitor itself, or, if the monitor is a part of a network of monitors, in a central memory that is a part of this network. Many different types and formats of data are stored in memory. Typical information might be: (1) patient demographic data, (2) digitized continuous recordings of the data being monitored, such as respiration and ECG, (3) recordings of data surrounding and including an event, such as prolonged apnea, (4) long-term trends in data such as respiration rate as a function of time over periods of time, such as 4, 8, or 24 hours, and (5) for home monitors, a time log of when the monitor was used.

6.4.2 Display

The second interface between the monitor electronics and a human is provided by the display. Its function is to provide the monitored information to clinicians through auditory and visual means. When an alarm condition is reached, a loud sound is produced to alert the caregiver that the infant needs attention. Visual displays on the monitor front panel provide a variety of information. This ranges from lights that flash with each detected breath or heartbeat through plots of the actual waveforms being monitored. Hospital monitors have complex displays that present a large variety of information for the clinician managing the infant. On the other hand, home monitors generally provide no more visual information than the flashing lights and a light to indicate when an alarm has sounded. There are often additional lights to indicate the source of the alarm such as apnea, bradycardia, or a loose lead.

Figure 6.11 — Examples of infant breathing signals: (a) regular breathing during quiet sleep; and (b) breathing with motion artifact.



6.4.3 Communication

Newer infant apnea monitors have the capability of communicating with other electronic equipment. In the case of the hospital monitor, individual instruments can be connected as a group into a computer network so that the information from each is available on the network. The network can also contain large memory devices for data storage so that clinicians at the nursing station or other locations can access the monitored information for individual patients. Home monitors also are getting networking capabilities. In this case, the monitor is not continuously connected to a network, but rather can be periodically downloaded into a network, via a telephone and modem, so that the data stored in its memory can be transmitted to a central location for analysis.

It is also possible for a monitor to communicate with other electronic devices through a removable memory. This memory, in the form of a card or cartridge, can be plugged into the monitor and used to record pertinent information. Before the memory of the card or cartridge is completely filled, the cartridge is removed and transported or mailed to a central location where the information can be downloaded and read on a computer system. In this way, the clinician responsible for the infant being monitored at home can keep track of the data being monitored without having to recover the entire monitor.

6.5 Secondary Measures of Apnea

Transthoracic electrical impedance apnea monitors respond to changes in geometry and resistivity of the chest and its contents. These changes can occur during obstructive apnea as well as during breathing, since breathing movements are still encountered and sometimes even exaggerated during obstructive apnea. Thus, a major limitation of transthoracic impedance apnea monitors is their inability to detect obstructive apnea. This, added to the previously mentioned problems of sensitivity to motion artifact and cardiogenic artifact, makes it necessary to consider physiologic variables in addition to measured breathing effort to improve the reliability of the monitor in detecting all kinds of apnea. One of two possible secondary variables should be used for this purpose.[7] An infant's heart rate will usually decelerate with prolonged apnea unless this effect is blocked pharmacologically. The oxygen in the arterial blood also decreases as the duration of apnea increases. Thus, by including either a method of measuring heart rate (a cardiac monitor), or of measuring arterial blood oxygen level (a pulse oximeter), it is possible to detect these changes and use them to provide an alarm in situations where the primary respiration apnea alarm fails to sound. The details of monitoring these variables are described in Sections 6.1 and 6.4. It is generally accepted that apnea monitors without one or the other of these variables are incomplete.

6.6 The Future

Although infant apnea monitors play an important role in the care of infants in the hospital, their role in home care is less certain. Studies currently underway will, hopefully, help to better define the role of this technology in the home. It will also be important to improve this technology in the future to avoid some of the problems associated with transthoracic impedance apnea measurement. New approaches to different types of sensors for measuring respiration are currently being studied. Strain gauges that sense breathing movement of the chest and abdomen are under development.[8] The inductance plethysmograph has been adopted for infant monitoring.[9] Some investigators believe that this technique is able to identify obstructive apnea as well as central apnea.

New signal processing is also being applied to infant apnea monitoring. Measures of heart rate and respiratory rate variability and their association with pathology are currently being investigated.[10] This type of sophisticated signal processing has the potential of being able to provide early warning of serious problems such as sepsis, as well as carrying out the traditional apnea monitoring functions. It is clear that there will be many opportunities and advances in infant apnea monitoring in the future.

6.7 References

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7.0 MECHANICAL VENTILATION

7.1 Pressure Control Ventilation

Pressure control ventilation is a technique in which the ventilator uses time to trigger the onset of a pressure waveform. The breath is terminated when a given pressure is reached and is reinstituted at a given time. Pressure control can either represent a pressure above the body surface pressure or below body surface pressure, thus defining either a positive pressure ventilator or a negative pressure ventilator. In pressure control ventilation, peak inspiratory pressure (PIP) and inspiratory time determine the tidal volume delivered by the ventilator. Increasing PIP while leaving all other parameters unchanged would be expected to improve oxygenation and also improve ventilation. Pressure control ventilation is the type of ventilation that has been used widely but generally coupled in the form of intermittent mandatory ventilation (IMV). Today, pure pressure control ventilation is used exclusively in patients who are paralyzed or sedated to the point where they do not breathe spontaneously.[1,2,3]

The techniques for using pressure control ventilation are very similar to those of IMV. The difficulty with positive pressure control ventilation is that its side effects are greater than seen with IMV. This is related to the fact that the number of breaths per minute is greater and there are no spontaneous respirations by the patient that improve venous return and cardiac output.

7.2 Intermittent Mandatory Ventilation

Intermittent mandatory ventilation was first used by Kirby et al. in 1971 to manage infants with hyaline membrane disease (HMD).[4] This system enables the infant to breathe spontaneously between mechanical breaths. The positive effect of this is to decrease arterial carbon dioxide partial pressure ($PaCO_2$), improve venous return, decrease the negative effects on cardiac output of positive pressure ventilation, and facilitate weaning of the patients. Intermittent mandatory ventilation has continued to be the primary mode of ventilating newborns.

Tidal volume delivered by the ventilator, as with positive pressure ventilation or pressure control ventilation, is determined by the PIP and inspiratory time. Flow rate in the ventilator circuit plays a small role depending on the level of peak inspiratory pressure. The effect of inadequate flow rate is that the set peak inspiratory pressure will be reached later in the cycle or not at all, and the patient will receive a smaller tidal volume during this cycle.

Theoretically, IMV allows positive pressure breaths to be prolonged; thus aids alveolar recruitment with less effect on $PaCO_2$ and cardiac output. This is seen with pressure control ventilation, since the patient can breath spontaneously between IMV breaths, thus improving venous return and $PaCO_2$. All conventional ventilators used in newborns now have IMV control. The major drawback to IMV is the frequent difficulty of synchronizing IMV and patient breaths. This reduces the tidal volume delivered to the patient which reduces minute ventilation, thus necessitating an increase in PIP to adequately ventilate the patient. The ultimate result is an increased risk for air leak, adverse effects on cardiac output, decreased venous return, and, potentially, intraventricular hemorrhage.[5,6,7] In this ventilator system, high ventilator rates may be

associated with inapparent positive end-expiratory pressure (PEEP) and air trapping, which may lead to similar problems seen with an increase in PIP.[8]

7.3 Clinical Applications

Ventilator variables used in managing various respiratory disorders are given in Table 7.1.

Table 7.1 — Ventilator Variables.

I. Peak Inspiratory Pressure (PIP)

Positive effects	Negative effects
1. Alveolar recruitment with improvement in oxygenation 2. Improved CO_2 removal 3. Decreased work of breathing 4. Reduced oxygen exposure	1. Barotrauma 2. Overdistension of lung with increased work of breathing and decreased PaO_2 3. Adverse effects on cardiac output 4. Adverse effects on cerebral circulation

II. Ventilator Rate

Positive effects	Negative effects
1. Improved ventilation (decreased $PaCO_2$) 2. Improved work of breathing 3. Improved oxygenation via increase in mean airway pressure	1. Air trapping associated with inapparent PEEP at high rates (> 60 per minute). Some ventilators, particularly the infant star, have eliminated this problem 2. Decreased tidal volume even with PIP maintained

III. Increased Inspiratory-to-Expiratory Ratio

Positive effects	Negative effects
1. Alveolar recruitment with improved oxygenation	1. Gas trapping 2. Increased risk of air leak 3. Increased $PaCO_2$

IV. Decreased Inspiratory-to-Expiratory Ratio

Positive effects	Negative effects
1. Decreased $PaCO_2$ 2. Decreased gas trapping 3. Decreased risk of air leak	1. Inadequate alveolar recruitment with adverse effect on oxygenation

V. Increase in flow rate - (alters slope of inspiratory limb more or less depending on ventilator)

Positive effects	Negative effects
1. Increased airway pressure and improve volume delivery 2. Decrease work of breathing between positive pressure breaths	1. Potential for increased turbulence in airway with resultant decrease in tidal oxygenation 2. Increased $PaCO_2$ 3. Decreased PaO_2 4. Airway injury

VI. Increased levels of PEEP

Positive effects	Negative effects
1. Alveolar recruitment maintained 2. Improved V/Q 3. Improved oxygenation	1. Adverse cardiovascular effects with potentially decreased tissue oxygen delivery 2. Increased $PaCO_2$ 3. Increased risk of intraventricular hemorrhage

7.4 Diffuse Alveolar Disease

The major goals of IMV in this disorder are to improve alveolar expansion, lung compliance, and ventilation/perfusion (V/Q) matching. Early institution of IMV is desirable prior to alveolar collapse. Once alveoli are collapsed, high PIP are required to open them and the risk of barotrauma is high. An initial PIP should be chosen that will demonstrate adequate chest wall movement. If there appears to be adequate chest wall movement, but the patient has a high $PaCO_2$ and asyncrony of breathing is not present, this generally suggests that the conducting airways are being dilated due to severe alveolar/saccular collapse. In this situation, increasing PIP, prolonging inspiratory time, and/or increasing rate would most likely improve oxygenation and ventilation. This type of patient is at extremely high risk for developing barotrauma. Once alveolar recruitment is achieved, as noted by increase in arterial oxygen partial pressure (PaO_2) and decrease in $PaCO_2$, ventilator weaning should begin. Fractional inspired oxygen concentration (FiO_2) should be reduced to 70% and then PIP should be reduced. Positive end expiratory pressure generally should be maintained unless there is evidence of increased lung volumes. Attention must be paid not to overwean patients like this, which will result in alveolar derecruitment with a decrease in PaO_2 and increased risk of barotrauma during the recovery stages.[9]

A common error in managing these types of patients with IMV is to aggressively wean PIP, resulting in a reduction of mean airway pressure due to the person having a low $PaCO_2$. Carbon dioxide diffuses much more rapidly than oxygen (O_2). Therefore, a low $PaCO_2$ does not necessarily mean a high lung volume. Most importantly, an assessment of lung expansion via X-ray prior to decreasing PIP is necessary. If the lung is poorly inflated, or a high FiO_2 (> 50%) is required, increasing PEEP would help prevent alveolar collapse and decrease tidal volume delivered, resulting in an increased $PaCO_2$. If end expiratory pressure is increased enough, PIP additionally could be decreased.

The PEEP required for patients with this disorder may be anywhere from 2 cm H_2O to 12 cm H_2O depending on the size of the infant and degree of alveolar collapse. Use of surfactant has generally reduced the need for PEEP to the 2 cm H_2O to 5 cm H_2O range. High PEEP levels 5 cm H_2O to 10 cm H_2O should be weaned rapidly once surfactant is given and overall lung inflation improves. Failure to do this may result in air leak, increased risk of IVH, and decreased cardiac output.

7.5 Nonhomogeneous Pulmonary Disease

7.5.1 Meconium Aspiration Syndrome

Patients with meconium aspiration syndrome fall into two categories: 1) diffuse alveolar disease with hazy lung fields and low lung volumes; these patients should be treated as noted above for diffuse alveolar disease; and 2) patchy lung disease associated with air trapping and atelectasis.

Patients who have aspirated meconium *in utero* and have significant meconium aspiration syndrome generally have been hypoxic *in utero*. These patients are likely to have persistent pulmonary hypertension (PPHN) of the newborn associated with their pulmonary pathology. Therefore, maintenance of adequate oxygenation, venti-

lation, and pH is critical. Assisted ventilation should be initiated in patients who require FiO_2 > 50% or demonstrate increasing O_2 requirements; have increasing alveolar carbon dioxide partial pressure ($PACO_2$) generally > 50; or steadily increasing $PaCO_2$, labored respirations, or evidence of severe PPHN. Institution of ventilation requires careful assessment. Ventilator parameters need to be adjusted to minimize V/Q mismatch. Due to their predilection for air trapping, most of these patients benefit from low rates, low PEEP (1 cm H_2O to 4 cm H_2O) and reduced inspiratory-to-expiratory (I:E) ratio to promote complete lung emptying. Hyperventilation, which may benefit PPHN in this type of patient, holds a significant risk for barotrauma and inflammatory lung injury. Alkalosis for management of PPHN would be better accomplished using exogenous base such as tromethamine (THAM) or sodium bicarbonate. The pulmonary status of these patients often changes from hour to hour, necessitating changes in strategy to suit the predominant pulmonary pathology. Increased PIP, PEEP, and inspiratory time for more diffuse atelectasis and decreased PEEP, decreased inspiratory time and decreased rate for air trapping.[10, 11] The use of alternative therapies, such as high-frequency ventilation (HFV) and extracorporeal membrane oxygenation (ECMO) need to be considered early for the sickest patients in this group.[12, 13]

7.5.2 Localized Pneumonia

Most neonatal pneumonias tend to be diffuse. Localized pneumonia may occur in association with staphylococcuss aureus and escherichea coli. Management is directed at obtaining adequate ventilation and oxygenation with minimal barotrauma. The normal lung when overexpanded, particularly from a tidal volume standpoint, is at risk for injury, so this must avoided. A true lobar pneumonia is associated with a significant intrapulmonary shunt which leads to a relatively fixed PAO_2. Therefore, these patients should have their FiO_2 weaned and accept a PO_2 around 50 mmHg. A PIP and PEEP that provides an acceptable $PaCO_2$ < 50 mmHg with normal pH 7.3 or greater should be accepted rather than striving for a $PaCO_2$ in the low 40 mmHg range. The goal is to minimize barotrauma by minimizing overdistension of the normal lung.[14]

7.5.3 Pulmonary Hypoplasia

Pulmonary hypoplasia patients may be divided into two groups — those with diffuse hypoplasia (e.g., decreased amniotic fluid, bilateral pleural effusions, compression secondary to abdominal masses, or ascites) or focal hypoplasia (e.g., generally unilateral secondary to d-hernia, cystic adenomatoid malformation, or intrathoracic masses). Great care must be taken to avoid injury in these patients. Diffuse hypoplasia is treated with PIP and PEEP adequate to provide a PAO_2 of approximately 50 mmHg in 70% oxygen or less. The PIP+ rate should be directed at a $PACO_2$ of approximately 50 mmHg. An effort to achieve normal blood gases is likely to injure the lung, resulting in the need for increased PIP and further injury. High-frequency ventilation, ECMO, or liquid ventilation should be considered early in patients not responding to continuous mechanical ventilation (CMV). In focal hypoplasia, PPHN is often a significant part of this disorder.[15] The goal of IMV is to provide adequate ventilation and oxygenation with minimal injury of the normal lung. Generally, this is

best accomplished by using low PIP, high rates 40 to 60, and PEEP adequate to prevent alveolar collapse — 2 cm H_2O to 3 cm H_2O for patients with normal lung compliance and 4 cm H_2O to 8 cm H_2O for patients with poor lung compliance. The avoidance of high tidal volumes (if the nonhypoplastic lung is normally compliant) will help prevent barotrauma to this lung. The early use of alternative modes — HFV, ECMO, nitrous oxide (NO) and possibly liquid ventilation — may lead to better success with less long term lung injury.[16, 17]

7.5.4 Bronchopulmonary Dysplasia

Patients with bronchopulmonary dysplasia (BPD) fall into two categories: 1) cystic BPD with areas of atelectasis and hyperinflation; and 2) hazy BPD associated with low lung volumes. Ventilatory management of patients in the first category is accomplished best with large tidal volumes, low PEEP (2 cm H_2O to 3 cm H_2O) and long expiratory times to minimize air trapping. A subset of these patients, however, often does better with high PEEP (4 cm H_2O to 8 cm H_2O). This appears related to the stabilization of airways, thereby preventing premature airway closure and its associated air trapping. Pulmonary function tests can be helpful in determining the best pattern for these patients. Patients in the second category do best with higher PEEP (4 cm H_2O to 6 cm H_2O) and longer inspiratory times. These patients often may be weaned to nasal continuous positive airway pressure (CPAP). In both types of patients, the prevention of hypoxia and hypercarbia is the major therapeutic goal. This appears to improve weight gain and reduce the incidence of corpulmonale, a major cause of late death in these patients.[18]

7.6 Continuous Positive Airway Pressure

Continuous positive airway pressure for the newborn was first described by Gregory et al. in 1971.[19] Most individuals managing newborns believed the institution of continual distending pressure marked a turning point in the management of newborns with HMD. Positive pressure ventilation had been used with little success in the late 1950s and early 1960s. However, the use of CPAP-PEEP in many centers resulted in a marked improvement in survival. As with most techniques, some controversy has existed. In the management of lung disorders, particularly those associated with low lung compliance, it remains a mainstay of therapy. The effective use of CPAP requires a thorough understanding of the pathophysiology of the lung disorder being managed along with the benefits and potential risks of CPAP.

The benefits of CPAP include increased functional residual capacity (FRC), decreased right-to-left intrapulmonary shunt, increased alveolar oxygen partial pressure (PAO_2), and decreased work of breathing. The risks of CPAP include increased $PACO_2$ until FRC increases, and, if overdistention of the lung occurs, decreased compliance, increased work of breathing, increased pulmonary artery pressure, increased right-to-left cardiac shunt via patent foramen ovale and patent ductus arteriosis, and increased barotrauma.

Table 7.2 — Advantages and Disadvantages of Using Prongs.

I. Short Prongs

Advantages	Disadvantages
1. Easy to insert 2. Less occlusion of prongs with secretions 3. Personnel able to easily detect occlusion of prongs 4. Potentially less risk of infection in nasopharynx	1. Dislodges easily resulting in loss of CPAP and oxygen delivery to the patient, with loss of alveolar recruitment 2. May irritate the patient, resulting in a compromise of minute ventilation and oxygenation

II. Long Prongs

Advantages	Disadvantages
1. Delivers CPAP continually to laryngeal area 2. Does not dislodge easily, so CPAP and O_2 remains constant 3. May give positive pressure breaths via the prongs	1. May irritate the nasal passage causing increased production of mucus and edema formation, complicating breathing by the patient when the catheters are discontinued 2. Potential increased risk of infection with mucus buildup in the nasopharynx 3. Potential for obstruction of prongs with loss of oxygen and pressure delivery that cannot be visualized by caretakers 4. Must be removed periodically to clean, resulting in loss of positive pressure to lung 5. May deliver increased air to esophagus in small babies 6. Cannot be suctioned with standard suction catheter

III. Endotracheal tube placed in the nasopharynx

Advantages	Disadvantages
1. Delivers CPAP to laryngeal area 2. Does not dislodge easily; CPAP and O_2 delivery remain constant 3. May give positive pressure breaths via tube 4. Plugs less easily than smaller dual prongs 5. Can suction through tube using a standard suction catheter without requiring removal of tube	1. May irritate the nasal passage causing increased production of mucus and edema formation, complicating breathing by the patient when the catheters are discontinued 2. Potentially increased risk of infection with mucus buildup in the nasopharynx 3. Potential for obstruction of prongs with loss of oxygen and pressure delivery that cannot be visualized by caretakers 4. Must be removed periodically to clean, resulting in loss of positive pressure to lung 5. May deliver increased air to esophagus in small babies 6. May cause nasal septal erosion

IV. Endotracheal tube placed in the trachea

Advantages	Disadvantages
1. Most effective delivery of pressure to the airway 2. Does not easily dislodge 3. Pressure delivery and oxygen delivery remain constant 4. Can suction using standard suction catheter 5. May give positive pressure breaths	1. Requires tracheal intubation with increased risk of infection 2. Increased work of breathing if positive pressure breath not used

Continuous positive airway pressure can be delivered by numerous techniques including: 1) tight fitting mask, 2) head box with neck seal, 3) nasal prongs short, 4) nasal prongs long, 5) endotracheal tube placed in posterior pharynx, and 6) endotracheal tube placed in trachea. The first technique is generally used in the delivery room, or for diagnostic purposes to differentiate between congenital heart disease and pulmonary disease. The second technique is basically no longer used. The use of nasal prongs was first described in 1973[20] as a means to manage patients with HMD without intubation. The original prongs used were approximately 1-in. long. The fact that the neonate is an obligatory nose breather enables nasal prongs to be used effectively. Continuous positive airway pressure may be increased to 15 cm H_2O using these types of prongs. The advantages and disadvantages are given in Table 7.2.

7.6.1 Diffuse Alveolar Disease in Continuous Positive Airway Pressure

The pathophysiologic findings in diffuse alveolar disease are low compliance, decreased FRC, generally homogeneous infiltrates, short expiratory time constants, and surfactant deficiency or dysfunction. Hyaline membrane disease, Group B strep pneumonia, adult respiratory distress syndrome (ARDS), and pulmonary hemorrhage are diffuse alveolar diseases, and would be expected to respond favorably to CPAP-PEEP. There is ample evidence in newborns that initial application of CPAP is associated with a decrease in lung compliance.[21, 22] Therefore, earlier use of CPAP, specifically prior to an increase of $PaCO_2$ to > 55 cm H_2O, would be expected to be more successful. The early application of CPAP additionally helps prevent alveolar collapse and maintain FRC enabling the patient to maintain their lung on the most efficient portion of the pressure volume curve. The amount of CPAP required is dependent upon the size, gestational age, and, most important, severity of lung disease. This could vary from as little as 2 cm H_2O to 4 cm H_2O to as much as 8 cm H_2O to 12 cm H_2O. The ideal CPAP is the level that results in the highest arterial alveolar oxygen ratio with minimal effect on cardiac output and cerebral venous return. In general, more CPAP is required when given by the nasal route than when given endotracheally. As a primary mode, CPAP appears to be least effective in the smallest and youngest gestational patients. A potential drawback of using nasal CPAP is that it delays giving the patient surfactant. Effective use of nasal CPAP is also complicated by apnea. This may be overcome by providing a backup rate to these patients using the longer nasal prongs or endotracheal tube. When using nasal CPAP, attention must be paid to the potential for worsening atelectasis. If, in spite of increasing CPAP levels, the FiO_2 is increasing, the $PaCO_2$ is increasing, and the X-ray shows significant atelectasis, recruitment with positive pressure ventilation is imperative. Once severe atelectasis occurs, recruitment with positive pressure ventilation is likely to result in significant pulmonary injury. These patients should additionally receive surfactant. The key to success with CPAP in these patients is early use, adequate pressures, backup ventilator rate as needed, and a change to positive pressure, ventilation, and intubation along with surfactant if blood gases are not improving.

7.6.2 Bronchopulmonary Dysplasia

Nasal CPAP can be useful in a subset of patients with BPD who tend to have problems with airway patency during expiration. This can be due to partial airway obstruction or potentially due to a degree of bronchomalacia present in these patients. The use of CPAP on these patients prevents premature closure of the airways and promotes adequate lung emptying while avoiding air trapping, which improves carbon dioxide removal. CPAP in particular with a backup rate may facilitate early extubation of these patients, thereby obviating the need for a tracheostomy. The major difficulty with using CPAP in these patients is that they tend to be somewhat irritable and often will dislodge the CPAP device or render it nonfunctional. In addition, if the CPAP device increases their irritability, this may have a negative effect on oxygenation and ventilation.

7.6.3 Extubation

The use of nasal CPAP to facilitate extubation of patients was first described by Engelke et al. in 1982.[23] This was expanded upon by Higgins et al. in a 1991 publication demonstrating its usefulness in patients weighing < 1 kg.[24] As noted by Andreasson et al.[25] Nasal CPAP appears to facilitate extubation by increasing oxygenation, reducing apneic episodes and elastic and resistive loads on the diaphragm. The effect of nasal CPAP on preventing apnea may be related to its effect on stinting the upper airway and preventing obstructive apnea, and also by improving FRC, preventing atelectasis, stabilizing the chest wall, and reducing the work of breathing. As previously mentioned, the additional advantage of nasal CPAP is that if the patient has apnea positive pressure breaths through the nasal prongs can be provided, thus avoiding reintubation of many of these patients.

7.7 Synchronized Intermittent Mandatory Ventilation

In an effort to improve asynchronous breathing that often occurs with IMV, synchronized intermittent ventilation (SIMV) was developed. At preselected time intervals, it always synchronizes an IMV breath with the patient's own breathing efforts. There is evidence that this technique results in more consistent flow volume relationships and tidal volumes, and, possibly, in expiratory volumes in patients. There is some evidence that this technique may improve oxygenation at lower PIP, and reduce the incidence of air leak, bronchopulmonary dysplasia, and intraventricular hemorrhage of newborn (IVH).[26] In addition, it may improve survival and reduce sedative requirements that many patients have while undergoing mechanical ventilation.

True SIMV is a technique that provides synchronized breath with only a portion of the patient's breaths. Another form of this kind of ventilation — assist control or patient-triggered ventilation — actually provides a mechanical breath for every patient-initiated breath. Whether one of these techniques is more beneficial than the other has yet to be determined in the various patient populations. There are multiple techniques by which SIMV can be generated, including a flow sensor, thoracic impedance sensor, hot wire anemometer, abdominal wall movement sensor, and esoph-

ageal pressure sensor. The problems associated with this type of ventilation deal predominantly with autocycling (which is inappropriate ventilator triggering due to artifactual signals), missing patient induced breaths, and asynchrony of supposed synchronized breaths. These techniques are all more sensitive in the larger patient (> 1200 gms). However, use in smaller patients appears to be possible and may improve as these devices evolve. How much of an improvement this technique will make on the outcome on patients remains to be defined. A recent randomized trial by Bernstein et al.[27] at six centers examined the difference in survival, IVH and pharmcological paralysis and time on assisted ventilation for patients in three birthweight categories: (< 1 kg, 1 kg to 2 kg, > 2 kg). There was no difference in these factors except in the greater than 2 kg group. In the less than 1 kg group, there was less need for supplemental oxygen at 35 weeks corrected age.

The conclusion was that SIMV compared to IMV in sick newborns can improve oxygenation, shorten the duration of ventilation, and reduce chronic lung disease. It is clear that all new generation neonatal ventilators will have this mode available as part of the ventilator. The basic strategies employed for the various pulmonary pathology between SIMV and IMV would be exactly the same, with, of course, the difference being that synchronization of breaths would be occurring with SIMV and the potential for weaning the ventilator earlier is possible.

SAVI, or Synchronized Assisted Ventilation in Infants, was described by Visveshwara et al. in 1991.[26] This is a technique of assisted control ventilation as each patient initiated breath is assisted. Synchronization is accomplished by a modification of thoracic impedance. The output of a cardiorespiratory monitor using a specially built synchronizer is coupled to a Seachrist neonatal ventilator. Employing this technique, Visveshwara et al. studied 110 infants. In 22 infants weighing <850 gms the duration of ventilation was significantly less. In 40 patients weighing 450 gms to 1250 gms the duration of oxygen therapy and progression of IVH from Grade I - II to III - IV were less but not statistically lesser.

7.8 Pressure Support Ventilation

Pressure support ventilation is a relatively new form that is present on most new microprocessor-driven adult ventilators. In the pressure support mode, the patient triggers the ventilator with a spontaneous breath, at which time a preset pressure is reached and maintained until the patient's inspiratory flow decreases to a preselected limit. This technique was developed to reduce the work of breathing and the negative effects of positive pressure ventilation. To date, this technique has not in its true form been used in the neonate. However, IMV is frequently used with a peak pressure that does not deliver a full tidal volume in many patients; the patient actually augments this breath, which would be a form of pressure support ventilation. Whether the new ventilators will be sensitive enough to provide this technique to the neonate in its pure form remains to be seen. Also, whether this technique offers any benefit to the neonate requires some study.

7.9 Volume Ventilation

Volume ventilators were used originally in ventilating babies during the 1950s and 1960s. The major problem with volume ventilation was the loss of delivered volume to the patient in the compressibility of the ventilator and the distensibility of the tubing going to the patient. It was not unusual, for instance, when using an MA1 ventilator to ventilate a baby, to require in a newborn with very poor lung compliance a tidal volume set in the 400 cc to 500 cc range for a 1 kg infant. Once compliance improved it was very likely that barotrauma would occur as a greater volume would be delivered to the patient. This made the use of volume ventilators more difficult and they lost favor very quickly in the neonatal sector. The more recent development of ventilators with less compressible volume and those which actually measure volume displacement at the airway should make these devices more useful in the neonatal patient. The theoretical advantages of volume ventilation are:

- stabilization of lung volume;
- improved ventilation perfusion;
- stabilization of cerebral blood flow; and
- decreased air leak.

The theoretical disadvantages are:

- barotrauma;
- poor control of volume delivered; and
- not available for small prematures.

Recently, limited studies have been performed using volume ventilation in the newborn. Since some of the ventilators became available, the availability of this data will increase the likelihood of an investigation. It remains to be seen, however, how effective or how much reduction in lung injury can be accomplished using volume ventilation versus the present pressure type of ventilation.

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8.0 HIGH-FREQUENCY VENTILATION

High-frequency ventilation (HFV) is a unique form of assisted ventilation designed to reduce lung injury, and includes any mode of ventilation that supports gas exchange using small tidal volumes and high ventilatory rates. During HFV, the cycle of inflation and deflation associated with conventional mechanical ventilation is reduced. The avoidance of high lung volumes prevents overinflation of the more compliant lung units and the avoidance of low lung volumes prevents collapse of the less compliant lung units. Ventilation-perfusion matching improves, dead space volume decreases, and gas exchange is maintained with less lung injury.[1]

8.1 *Theory of How High-Frequency Ventilation Prevents Lung Injury*

The association between air leak syndromes and the use of high pressures is well established. A recent review suggests that changes in lung volume may be more important than changes in airway pressure in the propagation of lung injury.[2] When tidal volume is limited by casting the chest wall, the use of high airway pressures does not produce as much damage as when tidal volume is not limited.[3] Thus, the term barotrauma may be replaced by the term volutrauma.[4]

In animals with normal lungs, large tidal volume ventilation can damage the pulmonary capillary endothelium, alveolar and airway epithelium, and basement membranes.[2] This mechanical damage causes fluid, protein, and blood to leak into the airways, alveoli, and lung interstitium. The development of pulmonary edema and surfactant dysfunction impairs gas exchange; lung inflation and compliance decrease; and dead space volume and airway resistance increase. Higher levels of ventilatory support are required to support adequate gas exchange, and this causes more lung damage. Failure to interrupt this sequence can lead to progressive respiratory failure, severe pulmonary morbidity, and death. In addition, mechanical forces also influence cellular function. Lung inflation promotes type II cell secretion of surfactant, and cyclical mechanical deformation of fetal lung fibroblasts stimulates cell replication.[5] In neonates born prematurely, the early introduction of large tidal volume breathing may permanently change lung structure, function, and growth potential.

In animal models of hyaline membrane disease (HMD) and adult respiratory distress syndrome (ARDS), HFV prevents the propagation of lung injury by supporting adequate gas exchange with small tidal volumes.[1] Lung volume is held above functional residual capacity (FRC) by the use of a constant distending pressure determined by end-expiratory or mean airway pressure. Ventilation is accomplished at small tidal volumes and the cycle of lung inflation and deflation associated with conventional ventilation is reduced. Conceptually, HFV allows the use of high end-expiratory pressures without requiring the use of high PIPs to maintain ventilation. Avoiding lung overinflation and underinflation are both important goals of HFV.

The beneficial effects of HFV are dependent on optimizing lung volume and maintaining functional residual capacity. Early studies evaluating the use of high-frequency oscillatory ventilation (HFOV) in animals with HMD showed that use of lower mean airway pressures than those used on conventional ventilation were associated with progressive hypoxia.[6,7] At autopsy, the lungs of these animals were noted

to be severely atelectatic and noncompliant.[6] Adult animal models of ARDS show that atelectasis is associated with increased lung inflammation and lung damage. Subsequent animal studies have shown that optimizing mean lung inflation and ventilation-perfusion matching improves gas exchange, normalizes the pattern of lung inflation and reduces lung injury.[8,9,10] In the treatment of HMD, most authors suggest the use of relatively high mean airway pressure to recruit lung volume, followed by judicious weaning of the mean airway pressure.[1,9,10] Once lung volume is recruited and oxygenation improves, mean airway pressure can be reduced to levels that are lower than that required in control animals treated with conventional ventilation.[9,10,11]

Another important difference between HFV and conventional ventilation is the distribution of gas transport. During conventional ventilation, the distribution of gas transport is primarily effected by the combination of respiratory system resistance and compliance. In patients with lung disease, alveolar ventilation is higher in lung units with lower resistance and higher compliance when compared to units with high resistance and low compliance. Thus, the more normal units are cycled through larger volume changes and may be injured. During HFV, the distribution of gas transport appears to be more uniform, but is affected by tidal volume, frequency, respiratory system mechanics, and the uniformity of the lung disease.[12]

Animal studies have failed to define an optimal combination of tidal volume and frequency for ventilation with high-frequency ventilators.[13] Studies designed to find this combination are complicated by the fact that tidal volume delivered to the trachea is small, difficult to measure, and frequency-dependent. As frequency is increased, the tidal volume delivered to the trachea across a small-lumen endotracheal tube decreases. The degree of volume loss is dependent of the mode of HFV being used, mean airway pressure, and respiratory system impedance.[13] At present, there is no data comparing the effectiveness of the use of different tidal volumes and frequencies in the prevention of lung injury. Mathematical models suggest that optimal frequency shifts to higher frequencies (10 Hz to 20 Hz) as lung compliance decreases, and to lower frequencies (1 Hz to 5 Hz) as airway resistance increases.[12] Future research may define disease-specific frequencies and tidal volumes that maximize uniformity of gas transport and minimize the pressure (or volume) cost of ventilation.[12] In general, frequency is set at the initiation of HFV and is not varied during the course of treatment.

8.2 *Types of High-Frequency Ventilation*

8.2.1 Classification

There are several types of HFV. Each type of high-frequency ventilator and the specific strategies suggested for its safe use are unique; published results on the use of one type of HFV cannot be generally applied. Most of the data on the use of HFV in the U.S. has involved one of five high-frequency devices or one of its precursors: SensorMedics 3100A, Humming II, Bunnell Life Pulse, Infant Star HFV, and Programmable Volumetric Diffusive Respirator.[1]

High-frequency ventilators can be divide into four major groups: high-frequency jet ventilation (HFJV), high-frequency flow interruption (HFFI), HFOV, and hybrids. The unique feature of HFJV is that the high-frequency breath is delivered directly to the trachea through a special multilumen endotracheal tube. Pressure changes during HFJV are monitored within the trachea, and the expiratory cycle is dependent on the passive recoil of the respiratory system. High-frequency flow interrupters are similar to jet devices in that the expiratory cycle is passive. In contrast to HFJV, HFFI delivers the high-frequency breath and monitors pressure changes proximal to the endotracheal tube. As the name implies, HFOV oscillates gas in the patient circle. Each high-frequency breath consists of an active inspiratory and expiratory phase. Animal experiments suggest that an active exhalation phase may reduce the potential for gas trapping.[14] As with HFFI, pressure changes during HFOV are monitored at the proximal end of the endotracheal tube.

There are no clinical comparisons between different types of HFV. Each type of HFV has its own potential risks and theoretic benefits. The physician caring for patients treated with a specific type of HFV must know the limitations and the appropriate use of the device.

8.2.2 Problems with Pressure Monitoring

During conventional ventilation (rate <60), the pressure transmitted across the endotracheal tube to the trachea and down the airway to the alveoli is similar in form and amplitude to that measured proximal to the endotracheal tube. During HFV, measurements of ventilator pressures made proximal to the endotracheal tube do not accurately reflect tracheal or alveolar pressures. Figure 8.1 show changes of an idealized pressure waveform as it is transmitted to the alveolus. In healthy adult rabbits ventilated with HFOV, pressure transmission across a 3.0 mm-endotracheal tube was significantly attenuated.[15] At 15 Hz, the alveolar pressure swings were less than 10% of the pressure measured proximal to the endotracheal tube.[15] The degree of pressure amplitude attenuation is dependent on frequency, respiratory system impedance, and endotracheal tube size. Mean airway pressure measured proximal to the endotracheal tube is more accurate than measurements of pressure amplitude, but is also influenced by ventilator settings, respiratory system impedance, and endotracheal tube size. In some settings (e.g., I:E ratio> 1:1, or near the lung's resonance frequency), the mean pressure measured proximal to the endotracheal tube may be less than the mean pressure in the lung.[15] In other settings, (e.g., I:E ratio> 1:2, or when using large pressure amplitudes), the mean pressure measured proximal to the endotracheal tube may be greater than the mean pressure in the lung.

During HFJV, pressure is delivered to and monitored in the trachea. Thus, the attenuating effects of the endotracheal tube on pressure transmission are avoided. However, the effects of respiratory impedance and ventilator frequency on pressure transmission from the trachea to the alveolus are similar to those discussed for HFOV.[16] Pressure measurements made during different types of HFV and during conventional ventilation are device specific, and calculations based on these measurements (e.g., oxygenation and ventilation indices) should not be compared across different types of assisted ventilation.

Table 8.1 — Summary of Clinical Trials in Premature Infants with Respiratory Distress Syndrome.

Study cited	Number studied		Mean age enrolled (hrs)		Mean birth weight (kg)	
	CV	HFV	CV	HFV	CV	HFV
HIFI[24]	346	327	5.8	6.1	1.083	1.092
Carlo[25]	20	20	20	22	1.47	1.48
Clark[26]	26	30	7	9	1.08	1.08
HIFO[27]	90	86	22	21	1.744	1.732
Ogawa[28†]	46	46	2	1.7	1.258	1.243

Study cited	Mortality		Intraventricular hemorrhage (3,4)		Oxygen needed > 28 days	
	CV	HFV	CV	HFV	CV	HFV
HIFI[24]	60 (17)	60 (18)	63 (18)	84 (26)*	141 (41)	130 (40)
Carlo[25]	3 (15)	3 (15)	NR	NR	4 (20)	3 (15)
Clark[26]	3(12)	5(17)	6(23)	6(20)	17 (65)	9 (30)*
HIFO[27]	3 (3)	7 (8)	2 (2)	6 (7)*	NR	NR
Ogawa[28†]	1 (2)	0	1 (2)	2 (4)	15 (32)	17 (37)

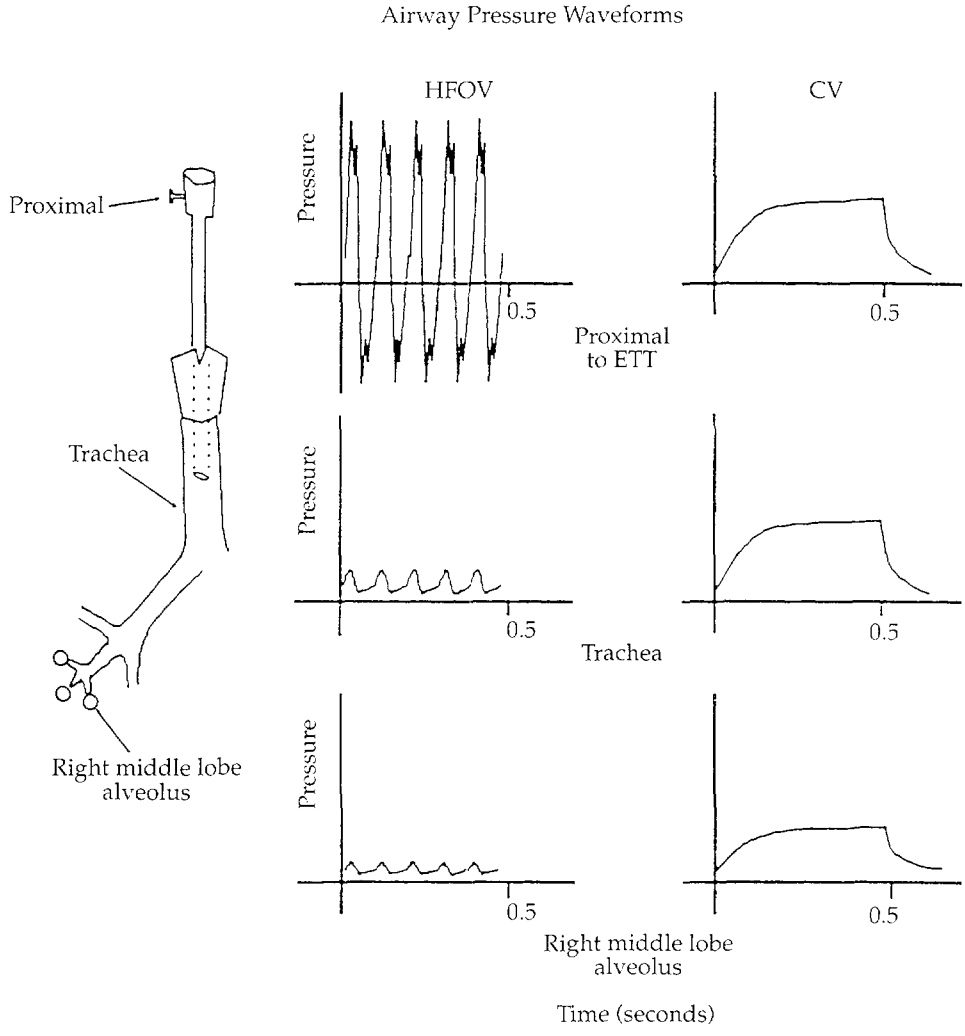
Data listed as N (%).

* P <0.05 HFV compared to CV.

†Study done after surfactant was approved for general use.

HFV, High Frequency Ventilation; CV, Conventional Ventilation; NR, not reported.

Figure 8.1 — Differences in pressure transmitted from the ventilator to the alveolus for high-frequency oscillatory ventilation (HFOV) and conventional ventilation (CV). These changes reflect those that occur across a 3.0 French endotracheal tube in adult rabbits with normal lungs. (from Null DM, in *Neonatology For the Clinician*, 1993.)



8.3 Use of High-Frequency Ventilation in Premature Neonates

8.3.1 Animal Studies of Hyaline Membrane Disease

Animal studies of the use of HFV in the management of HMD have produced exciting results. In the premature baboon model of HMD, HFOV reduces the occurrence of air leak, prevents the evolution of HMD, promotes uniform lung inflation, and improves gas exchange and lung mechanics.[8,17]

8.3.1.1 Prevention of Lung Injury

In rhesus monkeys with HMD, HFOV improves gas exchange and reduces exudative alveolar edema.[18] When compared to conventional ventilation, HFOV reduces the amount of inflammatory mediators (thromboxanes and platelet activating factor) and the number of leukocytes recovered in lung lavage samples recovered from animals with acute lung injury.[8,19]

High-frequency oscillatory ventilation is most effective in the treatment of surfactant-deficient animals when it is applied early and with a strategy designed to recruit and maintain lung inflation. Use of HFOV after 8 hours of conventional ventilation improves gas exchange and lung inflation when compared to continued use of conventional ventilation.[20] However, this relatively late use of HFOV is not as effective in reducing the pathologic findings of acute lung injury as the use of HFOV immediately after delivery.[20]

Equally important is the use of a HFOV strategy that optimizes lung inflation. In surfactant-deficient adult rabbits, the beneficial effects of HFOV occur only if lung volume is maintained at a level that prevents the development of significant atelectasis.[9] Lung overinflation is also dangerous because it can cause significant lung injury and compromise cardiac output.[8,11] Defining optimal mean lung volume is difficult during all forms of assisted ventilation and remains an important subject for future research.

8.3.1.2 Use of High-Frequency Ventilation with Surfactant

Data on the combined use of HFV and exogenous surfactant indicates a synergistic effect in reducing ventilator-induced lung injury. Proteinaceous alveolar edema in monkeys with HMD is reduced by both HFOV and exogenous surfactant, but the combination results in the least amount of edema.[18] When compared to administration of surfactant with conventional ventilation, the use of surfactant with HFOV improves gas exchange[9,21] and pulmonary mechanics,[9] and increases the phospholipid quantities recovered from lung lavage fluid in surfactant-depleted rabbits.[9]

Although animal studies show that surfactant and HFV synergistically reduce lung injury, it is unclear whether the use of HFV improves the distribution of exogenous surfactant within the lung. In premature lambs, HFOV did not improve the

distribution of surfactant given at birth. However, HFOV did improve oxygenation and alveolar expansion better than conventional ventilation in animals given surfactant after 30 minutes of assisted ventilation.[22] In premature rabbits, HFOV did not improve the distribution of surfactant regardless of the timing of surfactant treatment.[23] The differences in the findings of these studies may reflect differences in surfactants used, the type of HFV and conventional ventilation strategy used, and the animal model.[23]

8.3.2 Human Studies of Hyaline Membrane Disease

Clinical trials comparing the use of HFV and conventional ventilation in neonates with HMD are not as compelling as animal data (Table 8.1). The HIFI study group reported that the use of HFOV in the treatment of HMD was not effective in improving survival or reducing the incidence of bronchopulmonary dysplasia.[24] When compared to conventional ventilation, HFOV was associated with a small but significant increase in the occurrence of grades 3 and 4 intraventricular hemorrhage, periventricular leukoencephalomalacia, and pneumoperitoneum. Similarly, Carlo et al.[25] were unable to show any benefit from the use of HFJV in neonates with respiratory distress syndrome. Although gas exchange was supported at lower pressures, mortality, the incidence of air leaks, bronchopulmonary dysplasia, intraventricular hemorrhage, and treatment failure did not differ significantly between the treatment groups.

Two recent studies show different results (Table 8.1). Clark et al.[26] randomly assigned neonates to HFOV until extubation, conventional ventilation, and HFOV for 72 hours followed by conventional ventilation. Patients treated with HFOV until extubation had a lower incidence of chronic lung disease at 36 weeks postconceptional age than patients treated with conventional ventilation. There was no difference in the occurrence of chronic lung disease in patients treated with HFOV for 72 hours followed by conventional ventilation and patients treated with conventional ventilation. The rates of air leak, death, and intraventricular hemorrhage were not different in the three groups. The authors concluded that the use of HFOV was as safe as conventional ventilation and might decrease the occurrence of chronic lung disease in premature neonates requiring assisted ventilation. They attributed their results to the use of an HFOV strategy designed to recruit and maintain optimal lung inflation; specifically, they used higher mean airway pressures and shorter inspiratory times than those used in the HIFI study.

Using a similar strategy, the HIFO group studied 176 premature infants with severe HMD.[27] In neonates who entered the study without air leak, patients treated with HFOV developed new air leak less often than neonates assigned to continue on conventional ventilation (42% vs 63%, p=0.029). There was no difference between the two groups in the incidence of chronic lung disease or in the rate of survival. However, patients assigned to treatment with HFOV had a higher incidence of grades 3 and 4 intracranial hemorrhage.

The studies discussed above were performed before surfactant was approved by the Federal Drug Administration, and involved neonates who were treated with HFV relatively late (> 6 hours). Ogawa et al.[28] recently reported data on 92 premature neonates enrolled in a multicenter randomized study comparing the early use of HFOV to continued use of conventional ventilation. Most (78%) of the neonates in both treat-

ment groups received exogenous surfactant. Although HFOV was associated with improved oxygenation, there were no differences in outcome between the two treatment groups. The authors concluded that HFOV does not increase the risk of complications in neonates with respiratory distress syndrome treated with surfactant. Davis et al.[29] showed that rescue use of HFJV with surfactant can improve gas exchange in neonates with respiratory failure, but there are no controlled clinical trials evaluating either HFJV or HFFI with surfactant.

When compared to the data on the use of HFV in animals with HMD, the results of clinical trials are not as encouraging. The explanation of these contradictory results is most likely related to the heterogeneity of neonates with HMD, the timing and strategy of HFV employed, and the intercenter variability in neonatal management. Animal studies are designed so that confounding variables can be controlled. Experimental guidelines and strategies are strictly defined. In human studies, patient care is less uniform and it is difficult to control for all the potential confounding variables which include gestational age, infection, fluid management, ventilator strategy, race, and gender.

It is also difficult to compare the results of different clinical trials. As outlined in Table 8.1, each clinical trial used a different HFV device, initiated HFV at a different time, treated a different population of neonates, and used different HFV strategies. The impact of the differences on these results is difficult to evaluate. Finally, multicenter studies are often confounded by intercenter variability with some centers having better results than others.[18] In the era of surfactant replacement, the results of clinical trials do not yet prove that HFOV is more effective than conventional ventilation in the management of premature infants with HMD.

8.3.3 Human Studies - Pulmonary Interstitial Emphysema

Many of the preliminary evaluations of HFV involved preterm infants with air leak syndromes. Keszler et al.[30] reported a multicenter controlled trial comparing HFJV to conventional ventilation that showed that newborn infants with pulmonary interstitial emphysema were more likely to respond to HFJV than to continued conventional ventilation (61% vs 37%, $p<0.01$). High-frequency jet ventilation improved gas exchange at lower peak and mean airway pressures, and was associated with a more rapid resolution of pulmonary interstitial emphysema. When corrected for the crossover design, infants treated with HFJV had a better survival rate than neonates treated with conventional ventilation (65% vs 47%, $p<0.05$). The incidence of chronic lung disease, intraventricular hemorrhage, patent ductus arteriosus, and new air leak was similar for both treatment groups.

Uncontrolled rescue studies evaluating the efficacy of other forms of HFV in neonates with air leak syndromes show comparable results and indicate that HFV may be a valuable management tool in the treatment of these syndromes.[31-34] However, the reported rates of death (20% to 68%) and chronic lung disease (50% to 100%) are high in all these studies. Mortality and the occurrence of chronic lung disease are highest in neonates with birthweights <1.0 kg and with the most severe lung disease at initiation of HFV.[30,34] The association between air leak syndromes and bronchopulmonary dysplasia is well established, and these studies underscore the importance of prevention.

8.4 Use of High-Frequency Ventilation in Extracorporeal Membrane Oxygenation Candidates

8.4.1 Clinical Trials

Two studies have compared the use of HFV to conventional ventilation in extracorporeal membrane oxygenation (ECMO) candidates. Carlo et al.[35] retrospectively studied 37 neonates; 14 were treated with HFJV and 23 continued conventional ventilation. Neonates treated with HFJV were better ventilated at lower airway pressures, but there were no differences in survival (35% vs 36%) or the incidence of chronic lung disease in survivors (50% vs 40%). Clark et al.[36] reported a prospective randomized comparison of HFOV and conventional ventilation. In this study, HFOV was a more effective rescue tool than conventional ventilation. Sixty-three percent of the patients who did not respond to conventional ventilation responded to HFOV, but only 23% of the HFOV treatment failures responded to conventional ventilation. There were no differences between the two groups with respect to need for ECMO, ventilator or hospital days, chronic lung disease, or survival. Only 46% of the patients who met ECMO criteria required ECMO.

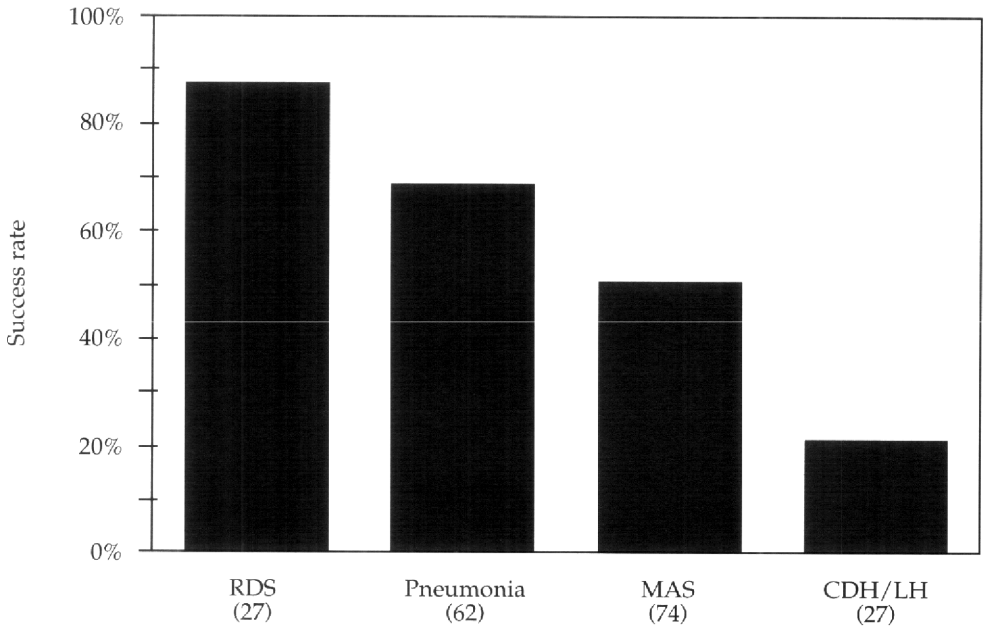
8.4.2 Extracorporeal Membrane Oxygenation Criteria During High-Frequency Ventilation

Extracorporeal membrane oxygenation is useful in the management of life-threatening respiratory failure.[37] However, there is debate over what is life-threatening respiratory failure.[38,39] The use of HFV in neonates considered candidates for ECMO has further complicated this definition.[35,36,40]

The ability of HFV to improve gas exchange in ECMO candidates is disease-specific. Baumgart et al.[41] reported their experience with neonates treated with HFJV before ECMO was available in their institution. Forty-five (62%) survived; when compared to nonsurvivors, survivors were better oxygenated (oxygenation index of 0.42±0.04 vs 0.30±0.03, $p=0.016$) and more often had respiratory distress syndrome (62% vs 21%, $p<0.01$). Survival in neonates with respiratory distress syndrome (82%) was significantly better than in neonates with meconium aspiration (38%) or congenital diaphragmatic hernia (33%). Infants in whom the oxygenation index ($Paw*FiO_2/PaO_2$) remained above 0.40 despite HFJV had a 68% mortality rate. Infants with meconium aspiration and an oxygenation index ≥0.40 had a 87% mortality rate.

Paranka et al.[42] reported similar disease-specific responses in ECMO candidates treated with HFOV (see Figure 8.2). High-frequency oscillation improved gas exchange in 88% of the neonates with RDS, 79% with pneumonia, 51% with meconium aspiration (MAS), and 22% with congenital diaphragmatic hernia (CDH/LH). Failure to show an improvement in the arterial-to-alveolar oxygen ratio (≥0.08) after 6 hours of HFOV was also predictive of a need for ECMO.

Figure 8.2 — Success rate of high-frequency ventilation in near-term neonatal ECMO candidates. The y-axis represents the percent of neonates who responded to high-frequency oscillation and avoided ECMO (number of responders/total number in the diagnostic group). (from Paranka MS. *Pediatrics*. 1995;95:400-404.)



These reports indicate that some neonates with severe respiratory failure should be offered a trial of HFV only when ECMO is available. Neonates with an oxygenation index of > 0.40 (or an arterial to alveolar oxygen ratio ≤0.05) and a diagnosis of meconium aspiration or congenital diaphragmatic hernia often do not respond to HFV.[41,42] In these types of patients, ECMO improves survival[37,40] and delayed referral to ECMO centers may increase morbidity and mortality.[43] Figure 8.2 shows the survival of neonates treated with ECMO to demonstrate the utility of ECMO in patients who fail to respond to HFV. Any patient whose oxygenation is poor despite a 4 to 8 hour trial of HFV should be considered for immediate transfer to an ECMO center. Such transfers can be complicated by the unavailability of HFV transport systems and difficulty in restarting conventional ventilation.

There have been no randomized trials comparing early ECMO to HFV in the management of neonates with respiratory failure. Although HFV may represent a less invasive form of therapy and should be tried before ECMO, it is important to define institutional and disease-specific ECMO criteria. Neonates should be offered the best and most definitive therapy without unnecessary delay. In neonates with labile pulmonary hypertension and meconium aspiration or diaphragmatic hernia, the therapy of choice may be ECMO. These questions await controlled clinical trials to provide the clinician with answers.

8.5 Use of High-Frequency Ventilation in the Pediatric Intensive Care Unit

Data on the use of HFV in children is limited to retrospective reports on the management of ARDS and/or air leak. Using a strategy aimed at improving lung inflation, Arnold et al.[44] reported that pediatric patients with respiratory failure who were treated with HFOV had a less chronic lung disease than those treated with conventional ventilation (21% vs 59%). Despite the use of high mean airway pressures, there was no evidence that HFOV decreased cardiac output. Rosenberg et al.[45] using both HFOV and HFFI, showed that these types of HFV could improve both oxygenation and ventilation. Survivors had more rapid and sustained improvement in oxygenation than that of nonsurvivors. Rescue studies also show that patients offered HFV early, after less than 10 days of conventional ventilation, are more likely to recover than those offered HFOV late. Studies evaluating HFJV have shown similar results;[46,47] survival rates ranged from 58% to 85% and were better than expected when compared to historical controls. In patients recovering from a Fontan procedure, Meliones et al.[48] showed that HFJV could be used to decrease pulmonary vascular resistance and increase cardiac index. This data suggests that HFV may improve the outcome of critically ill children. However, currently available HFV devices are not approved for use in children (> 5 kg) and should be used in the PICU only under approved study protocols.

8.6 Complications

Complications reported to be associated with HFV include hypotension, intraventricular hemorrhage, and necrotizing tracheobronchitis. The interaction of airway pressure with cardiac output is related to lung compliance and lung volume. The use of high airway pressure can cause lung overinflation, reduce venous return, increase pulmonary vascular resistance, and reduce cardiac output.[49] Animal and human studies show that, when used with a strategy that avoids lung hyperinflation, HFV does not reduce cardiac output.[11,44,50-52]

The etiology of intraventricular hemorrhage is multifactorial; thus, the association between HFOV and intracranial hemorrhage is difficult to assess. Two studies suggest that HFOV may slightly increase the risk of severe hemorrhages in premature infants with respiratory distress syndrome,[24,25] and two studies suggest there is no increased risk.[26,28] Comparing these studies is difficult because the patient populations are different. The authors of the HIFI study[24] suggested that the near constant mean airway pressure used during HFOV might restrict venous return and increase cerebral venous pressure. However, animal studies show that HFOV does not affect intracranial pressure[53] or cerebral blood flow.[11]

Tracheal injury is a potential complication of any form of ventilatory support that requires endotracheal intubation. Necrotizing tracheobronchitis is a severe form of tracheal injury that is often life-threatening. Early reports suggested that HFJV was associated with a high incidence of necrotizing tracheobronchitis.[54,55] More recent reports show that inadequate humidification of the inspired gas, decreased tracheal blood flow, and the use of high airway pressure are more important than the mode of ventilation in the etiology of this disease.[56-58] Studies comparing the use of HFOV and

conventional ventilation in the management of premature baboons show similar degrees of mild tracheal injury in both treatment groups.[59] In a recent clinical study, the occurrence of airway obstruction in neonates treated with HFJV was not different from the occurrence of airway obstruction in those treated with conventional ventilation.[30] The diagnosis of necrotizing tracheobronchitis should be considered in neonates with severe sudden airway obstruction because early recognition and treatment are life-saving.[60,61]

8.7 Conclusions

Ample data shows that HFV improves gas exchange in critically ill children in whom conventional ventilation has failed; however, the role it will play in improving outcome has not been determined. High-frequency ventilation may reduce pulmonary morbidity in premature neonates and it may reduce the need for ECMO in term neonates. Future research should define 1) disease-specific strategies that promote lung recovery and minimize lung injury; 2) the effect of HFV on exogenous surfactant delivery, function, and turnover; and 3) the long term outcome of neonates treated with this new mode of assisted ventilation.

8.8 References

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9.0 ADVANCED VENTILATION PRACTICES

9.1 Development of the Respiratory System

Understanding normal and abnormal neonatal respiratory physiology requires knowledge of the intrauterine and extrauterine timeline of lung development, which is also essential to the understanding of the lungs' response to various interventions to support respiration or stimulate lung growth. The appropriate choice of respiratory support modalities and the type of mechanical equipment used is often dependent on the neonate's gestational age.

9.1.1 Architecture of the Respiratory System

The respiratory system may be classified into three divisions: 1) the upper airways — nose, mouth, and trachea — have a relatively large diameter and are mainly extrathoracic; 2) the gas distributing system beginning from the mainstem bronchi to the terminal bronchiole; and 3) the acinus, considered the basic respiratory unit of the lung, is defined as the terminal bronchiole and its distal branches (respiratory bronchioles, alveolar ducts, and alveolar sacs) with their attached alveoli.[1]

Three types of airways comprise the tracheobronchial tree: 1) cartilaginous airways; 2) membranous bronchioles; and 3) gas exchange ducts,[2] which provides gas conduction and gas exchange. The cartilaginous airways include the trachea, the right and left mainstem bronchi, lobar bronchi, segmental, and subsegmental bronchi, and approximately five to six generations of small bronchi.

The membranous bronchioles have a diameter less than 1 mm and are devoid of cartilage in their walls. They include eight generations of airways including the primary, secondary, terminal, and respiratory bronchioles.

The gas exchange ducts and the first generation of gas exchange are also called alveolar ducts. The alveolar ducts are connected to alveolar sacs.

9.1.2 Lung Maturation

It is the beyond the scope of this discussion to present detailed coverage on embryogenesis. Standard texts are available (refer to reference #'s 1-4). It is important to be familiar with the embryonic germ cell layers in order to understand neonatal lung development. Shortly after conception, the fertilized egg undergoes rapid cellular proliferation to form a blastocyst. The cells of the blastocyst then reorganize to form a bilaminar germ disk which then converts to three germ layers by week 3 of embryonic life. The three germ layers, which are called endoderm, mesoderm, and ectoderm, give rise to the tissues and organs of the body: the ectoderm establishes the brain and structures of the central nervous system; the endoderm develops into major organs such as the heart, lungs, and liver and the mesoderm, the last germ layer to form, gives rise to cardiovascular, genitourinary, and lymphoid systems, as well as connective tissues.[2,5] The actual development of the lung is divided into four periods (see Table 9.1).[7]

Table 9.1 — Summary of Chronologic Development of the Lungs.

Development Period	Structural Development
Embryonic (conception to week 5)	Primitive lung bud, trachea, mainstem
Pseuoglandular (weeks 5 to 16)	Conducting airways, diaphragm
Canalicular (weeks 17 to 24)	Respiratory bronchioles, alveolar ducts type I and type II cells (pneumonocytes)
Terminal Sac (25 weeks to birth)	Alveolar number increases 20 million to 75 million
Postnatal growth (birth to 8 years)	Increases surfactant production, alveoli increases to > 300 million

9.1.2.1 Embryonic Period

The embryonic period begins with conception and continues through the fifth week. Development of the esophagus and laryngotracheal groove takes place early in this period.[8] The laryngotracheal groove then deepens to form a pouch at about 24 days. The pouch which is blinded is considered the first lung bud. It branches, forming two buds over the next few days. This leads to the development of the right and left mainstem branches.

9.1.2.2 Pseudoglandular Period

Extending from week 5 to week 16 is the second stage of lung development — the pseudoglandular period. It is during this period that the conducting airways develop. Segmental, subsegmental, and preacina airways develop with endings still blind.[9,10] By the end of the pseudoglandular period, all the major conducting airways including the terminal bronchioles have formed.

9.1.2.3 Canalicular Period

The canalicular period, the third period of lung development, extends from week 17 to weeks 24 to 26. Enlargement of the lung structures continues, and terminal bronchioles begin giving rise to respiratory bronchioles during this period. Each respiratory bronchiole has an alveolar duct and sac. Development of pulmonary capillaries begins. At around the 24-to-26 week period, two types of cells (type I and type II) pneumatocytes begin to appear.[6,9,10]

9.1.2.4 Terminal Sac Period

Stretching from week 24 to term of gestation, the fourth lung development period is known as the terminal sac period. During this period, early alveoli start to develop from alveolar ducts.[11] Further development of pulmonary vessels continues in association with alveoli. As the lung continues to mature, the number of alveoli increases (alveolarization). At 38 to 40 weeks there are approximately 20 million to 75 million alveoli in the newborn. This number grows to over 300 million by 8 years of age.[12,13,14]

9.1.2.5 Pulmonary Vessels Development

The development of the pulmonary vasculature coincides with the development of the airways.[13] During the embryonic period, the main pulmonary artery develops from the sixth branchial arch and feeds the developing lung bud. Pulmonary vasculature continues to proliferate along with the growth of the lung and is abundant at 26 to 28 weeks.[2] Prior to 26 to 28 weeks of gestation, about 35% of cardiac output enters the lungs. As the number and size of the pulmonary capillaries increases, cardiac output perfusing the lungs increases to approximately 7% to 10% at 38 to 40 weeks of gestation.

9.1.2.6 The First Breath

During the beginning of the birth process, the environment within the womb begins to change rapidly. Contraction of the uterus moves the fetus down the birth canal, thus decreasing placental blood flow and causing a change in the blood gas values of the fetus, which results in a change in the acid-base status. As the fetus travels down the birth canal, the chest is compressed, forcing lung fluid out of the upper airways and conducting airways, preparing the lungs to get their first breath.[2] The recoiling of the chest allows the introduction of the first breath into the lungs. To overcome the effects of surface tension, respiratory muscles must begin to contract to generate the successive inspiratory breaths. Lung fluid remaining in the alveoli is removed by drainage via the pulmonary capillaries and lymphatics. Lung fluid is replaced by air and, within a short time, air completely replaces the fluid. Within a few hours after birth, respirations become rhythmic; hence, adaptation to extrauterine life begins.

9.2 *Extracorporeal Membrane Oxygenation*

Extracorporeal membrane oxygenation (ECMO) is the term used to describe prolonged extracorporeal cardiopulmonary bypass via extrathoracic cannulation in patients with acute, reversible cardiac or pulmonary failure refractory to conventional medical or pharmacologic management.[15] Extracorporeal membrane oxygenation involves the use of a modified heart-lung machine to support gas exchange for a period of days or weeks until the lung has recovered.[15,27] This procedure provides rest for the cardiorespiratory system and prevents high oxygenation and positive pressure ventilation while allowing resolution and healing of reversible heart and lung disease.[16,17]

9.2.1 History of Extracorporeal Membrane Oxygenation

John Gibson is considered the father of extracorporeal circulation. During the 1940s and 1950s, he developed a heart-lung machine that could be used during vascular surgery.[18] The development of bubble oxygenators helped refine artificial lung technology in the 1950s.[19,20] Because direct gas interface was employed, an increased hematologic effect was observed, limiting its duration to not more than a few hours.[21] The invention of membrane oxygenators with a physical separation of the blood and gas phase minimized the problem of hemolysis and made long-term ECMO support possible.

The first trial of extracorporeal circulation in children through a bubble oxygenator was reported by Rashkind et al. in 1965.[22] Hill et al. reported the first successful use of prolonged extracorporeal bypass in 1972 in an adult with multiple trauma and respiratory failure.[23] Subsequently, the National Institutes of Health (NIH) sponsored a multicenter prospective, randomized ECMO study on adults with acute respiratory distress syndrome (ARDS), which was undertaken in 1975.[24] The overall outcome was not different from conventional mechanical ventilation (CMV) care, and the study was terminated. In retrospect, the dismal outcome of the adult ECMO study may have been due to the irreversible nature of adult pulmonary disease as manifested by fibrosis.[15]

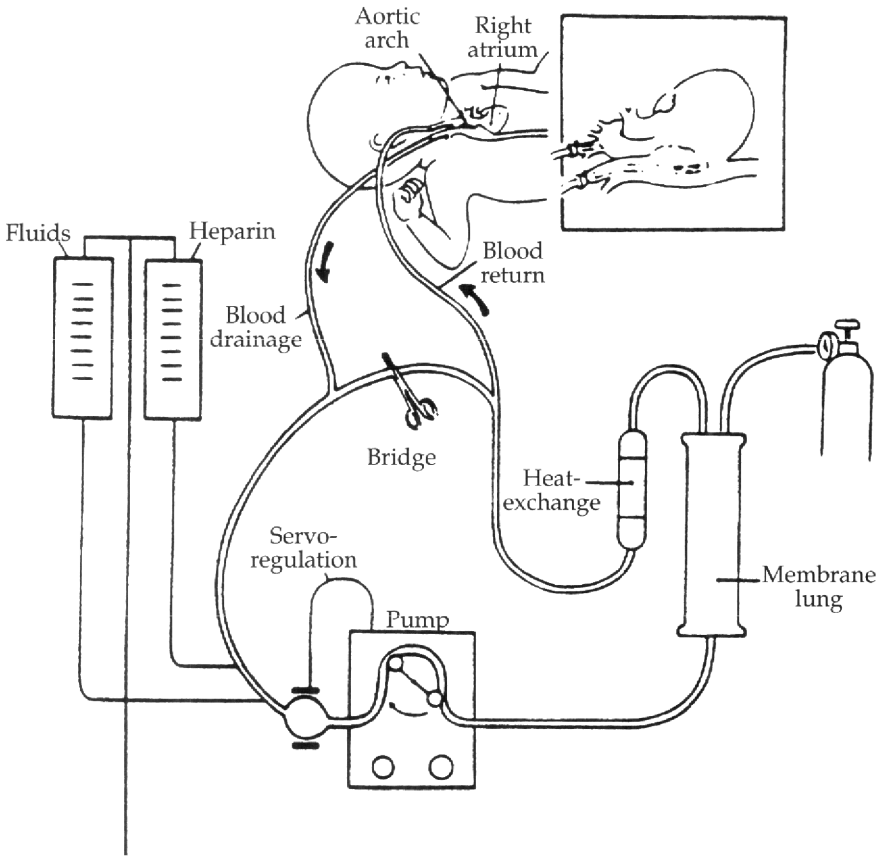
Meanwhile in 1975, Bartlett et al.[25] successfully demonstrated the use of ECMO in a neonate with a reversible pulmonary disease by performing the first successful application of venoarterial (VA) ECMO. The neonate was admitted with meconium aspiration syndrome (MAS). By 1982, the same group of researchers reported 55% success in 45 moribund neonates.[26,27] By the mid 1980s, neonatal ECMO became an established therapy for neonates at risk of dying from reversible respiratory distress syndrome. Many lives that otherwise would have been lost were saved. By the early 1990s, the number of neonates treated with ECMO in the United States averaged close to 1,300 per year, and the number of centers with active ECMO program has soared to 108.[28] So far, close to 10,000 neonates had been treated with an overall survival rate of 81%. However, the introduction of new, less invasive therapies such as high-frequency oscillatory ventilation (HFOV) may have stabilized, if not decreased, the use of ECMO.[29]

9.2.2 Extracorporeal Membrane Oxygenation Circuit

Currently, there are two kinds of ECMO regimen for perfusing infants. The veno-arterial (VA) route and the venovenous (VV) route. The VA route, the more commonly used technique, drains blood from the right atrium through a cannula advanced in the right atrium via the right jugular vein. Oxygen-rich blood is returned through the right common carotid artery in the ascending aorta (Figure 9.1). The large size of the carotid artery makes it an ideal choice in providing adequate blood flow to the aortic arch, thus making it a more common, preferable route of bypass. The VA has the advantage of providing support for both the pulmonary and cardiac systems. Two major risks inherent with this method of bypass are: 1) possible emboli (clot or bubble); and 2) the ligation of the carotid artery may adversely cause damage to the right hemisphere by affecting cerebral perfusion.[30]

The VV route supports the respiratory system so the interruption of the carotid artery is not needed. With this method, blood is drained from the right atrium via a right internal jugular vein and oxygen-rich blood is returned to the systemic circulation through a femoral vein.[31] If and when a cardiac problem arises, conversion from VV to VA ECMO can be performed.[32] The VV route is advantageous because it allows oxygen-rich blood to be perfused into the vein and spares the carotid artery. Oxygenated blood returns to the right side of the heart and lungs reducing the danger of arterial embolization. Perfusion of the pulmonary system with oxygen-rich blood may minimize pulmonary vascular resistance and will resolve pulmonary hypertension.[33] Many ECMO centers are increasingly using this route.

Figure 9.1 — Note position of venous and arterial catheters in right atrium and arch of aorta in this VA EMCO regimen. (from Bartlett RH, Andrews AF, Toomasian JM, et al. *Surgery*. 1982;92:425-433.)



9.2.3 Criteria for Use of Extracorporeal Membrane Oxygenation

Even though the criteria for ECMO use differ from center to center, every center uses some form of selection-based objective criteria predictive of potential mortality greater than 80%.[31] Bartlett et al. use the newborn insufficiency index which uses oxygen requirement, acidosis, and time plots to arrive at a score. Calculation is made from the neonate's pH and FiO_2 over 24 hours. The score is used to effectively measure high mortality rate. The induction of alkalosis as a treatment in some neonatal diseases has made this scoring system inapplicable.[34]

The alveolar-arterial oxygen gradient $P_{(A-a)}O_2$, greater than 620 mmHg for 6 to 12 hours was associated with mortality of 80%.[34] Alveolar-arterial gradient is a measure of alveolar insufficiency in transporting oxygen to pulmonary capillaries. The use of this criteria assumes that the patient is on 100% FiO_2.

Currently, the most widely used predictor of mortality is the oxygen index (OI) which takes into account the degree of oxygen requirement and the mean airway pressure (MAP) needed to achieve ventilation. An OI range between 40% to 50% is identified with 80% mortality.[36]

$$OI = \frac{(FIO_2)(MAP)\,x100}{PaO_2}$$

To receive ECMO, the neonate must have a reversible pulmonary pathology. Neonatal respiratory diseases that may fit this category are MAS, respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn (PPHN), congenital diaphragmatic hernia (CDH), and pneumonia/sepsis. The patient must weigh more than 2 kg and have a predicted mortality of greater than 80%. Exclusion criteria includes intraventricular hemorrhage greater than grade I, hypoxemic infants secondary to inoperative cardiac anomalies, diseases incompatible with life, and ventilatory support of more than 7 days.

The overall criteria is not without limitation. It is nonspecific for a given disease. The application assumes that the underlying pathology and clinical coarse are similar for all ECMO conditions.[37]

9.2.4 Extracorporeal Membrane Oxygenation Outcome

In the early 1980s, Bartlett et al. established the neonatal ECMO Registry in Ann Arbor, Michigan, called Extracorporeal Life Support Organization (ELSO). Its purpose is to serve as a voluntary data collection center for ECMO centers across the United States as well as other countries. Data of infants treated with ECMO is entered, indicating diagnosis, survival rate, mortality rates (Table 9.2), and are easily accessible. Survival with MAS has been the most successful (93%), followed by RDS (84%), and PPHN (83%). The survival rate of infants with CDH ranges from 52% to 60%. This discrepancy in survival rate may be due to duration of intervention and eligibility.[37] In the early days of ECMO, septic patients were excluded from ECMO.[38] The 76% success in patients with pneumonia/sepsis has caused revision in selection criteria.

Table 9.2 — The Distribution and Survival of Neonates Treated with ECMO From 1973-1993 According to Precipitating Diagnosis. Data is From Extracorporeal Life Support Organization (ELSO) Registry.

Diagnosis	Total	% Survival
MAS	3,547	93
RDS	1,074	84
PPHN	1,271	83
Sepsis	1,493	76
Air-leak	44	73
Other	348	77

9.2.5 Weaning From Extracorporeal Membrane Oxygenation

Once the patient is on ECMO, the plan is to limit the participation of the native lungs from gas exchange. The lungs are allowed to rest using low ventilatory settings (which differ from center to center). Prescribed ECMO flow is designed to support adequate gas exchange and blood pressure. The duration of ECMO exposure depends upon the nature of the disease and the condition of the patient. Patients diagnosed with CDH may require up to 12 days support, while patients with MAS may need 4 to 6 days of support. Weaning from ECMO is accomplished when clinical status has stabilized and lung compliance is improved. X-ray and blood gases are followed while the patient is placed on reduced ventilatory settings. Once the patient no longer needs ECMO support, decannulation is performed at the bedside. In some ECMO centers, surgical repair of the common carotid artery is done, thereby restoring blood flow.[39] This is only done if the VA route is used — the VV route needs no surgical repair and many ECMO centers have been increasingly using this route.

9.2.6 Complications of Extracorporeal Membrane Oxygenation

It is now well established that ECMO can be successfully employed to support at risk neonates and reduce their mortality rate. However, there are obvious complications and risks associated. Procedural risks such as ligation and cannulation of the right carotid artery and right internal jugular vein, heparinization, and exposure to blood products do occur.[36] Prevention of neurologic and pulmonary insult must be addressed. Extracorporeal membrane oxygenation-related morbidity has been impli-

cated even though it is unclear whether the damage is related to the ECMO process or the selection process, timing, hypoxia, or ischemia related to the underlying disease.[37] Reports indicating long-term neurologic insults ranging from moderate to severe have been assessed on patients treated with ECMO.[38-40]

Technical considerations regarding the design of ECMO circuitry is advancing; although safer, more user-friendly ECMO techniques are still unavailable. According to O'Rourke, virtually any part of the ECMO circuit and procedure deserves critical review.[37]

9.2.7 Future of Extracorporeal Membrane Oxygenation

Despite a legitimate concern regarding the use of ECMO to treat respiratory failure in neonates, ECMO has a definite place in the clinical arena. And as refined technology is implemented, the use of ECMO for populations that were previously excluded will need to be considered. The potential treatment group in the near future may include premature babies as well as pediatric patients. Extracorporeal membrane oxygenation is now a standard therapy in patients with PPHN who fail CMV. Recently, however, there has been a decrease in the number of patients with PPHN entering ECMO therapy. This coincides with the widespread use of exogenous surfactant. It now appears that early intervention with surfactant therapy reduces the need for ECMO. The role of exogenous surfactant for infants with respiratory failure due to MAS and sepsis is, however, unclear. Lotze et al. have reported that the use of surfactant significantly reduces the duration of ECMO in infants suffering from respiratory failure.[41] Recently, Carter et al. demonstrated that 46% of neonates suffering from acute respiratory failure and unresponsive to vigorous CMV could be successfully managed with HFOV without recourse to ECMO.[42] A perspective, randomized trial of HFOV by Clark et al. reported that HFOV was no more effective than CMV.[43,44]

The search for the ideal pulmonary vasodilator that could render blood flow to the lungs with little or no adverse side effect has been underway for 20 years. Nitric oxide (NO) may be the drug of choice. Published reports of the use of NO in neonates with PPHN indicate favorable outcome by improving pulmonary vasodilation without affecting systemic blood flow.[45] Administration of 10 ppm to 20 ppm in infants with PPHN by Kinsella et al. also resulted in improved oxygenation. All of these infants recovered without the need of ECMO.[46,47]

More promising approaches to the administration of vasodilators may include the administration of drugs like NO by perfluorochemical agents in liquid ventilation. Even though this approach may be a few years away, the future in the management of pulmonary vascular tone appears bright.[48]

9.3 *Surfactant: Natural and Synthetic*

The human lungs have a strong surface-active material, surfactant, which is necessary for the normal function of the pulmonary system. The lung is clearly a critical organ for early normal adaptation to extrauterine life. Therefore, adequate prenatal maturation of the respiratory system is an important aspect of intrauterine development. Lung maturation requires carefully controlled coordination of physiologic, anatomic,

and biochemical processes. The ultimate result of these maturational events is an organ that has a blood supply, and surface area, and is capable of metabolism in sustaining oxygenation and ventilation during the neonatal period and postnatal life. Of particular importance from the biochemical standpoint is the ability for rapid synthesis of surface-active phospholipids, which are necessary in maintaining normal lung function after birth.[49]

Information on the developmental biology of the respiratory system provides important insights into pulmonary dysfunction after birth, as well as an understanding of developmental disorders of the lung.[50-53] For example, RDS could not be fully appreciated from the standpoint of pathophysiology without a thorough understanding of the process of fetal lung maturity and the biology of pulmonary surfactant.

9.3.1 History of Surfactant

The major etiology of RDS in neonates has been linked to pulmonary surfactant deficiency. As a result, efforts have been devoted to investigating the biosynthesis and physiology of this phospholipid-rich substance. Advances in research have narrowed the gap from the laboratory to the bedside in enhancing the care of the very sick premature infant.

Over 60 years ago, surface forces acting at the air-fluid interface of the lung were described by Neergaard, thereby paving the way for experimental observation of the potential significance of pulmonary surfactant.[54]

About 25 years ago, studies on the pathophysiology of RDS and the nature of surfactant were conducted.[55,56] Soon after, lung surfactant was discovered from lung extracts and pulmonary edema foams. It was concluded that the death of premature infants and fetuses could be attributed to surfactant deficiency. This provided the groundwork for more rational approaches to the investigation and treatment of RDS. Greater understanding of the basis of pulmonary dysfunction in RDS and the role of surfactant also has helped refine techniques for the mechanical ventilation of the neonate.[53]

During the past 15 years, the shift in emphasis from the anatomic and physiologic studies to the study of fetal lung development toward biochemical approach of synthetic and natural surfactants was made, eventually leading to commercially available products.[57,58]

9.3.2 Origin of Surfactant

The role and nature of surfactant can only be appreciated if the developmental steps that lead to lung maturation are reviewed. An abbreviated classification of lung development is:[49,52,53]

- Embryonic phase — the first 5 weeks of life after conception; during this phase the formation of airways is initiated.
- Glandular phase — from 5 to 16 weeks of gestation, the lower conducting airways begin to form.
- Canalicular phase — weeks 17 through 26 of gestation.

- Terminal air sac period — the formation of the first respiratory units.
- Alveolar phase — begins in the perinatal period and continues through approximately 8 to 9 years of age.

Specific cell types begin to appear in the canalicular stages of development with the presence of cellular inclusions that accumulate within the respiratory epithelium. These cells are classified as type II pneumonocytes. There is a direct correlation between the presence of type II cells and the appearance of surfactant in lung extracts. In humans, the type II pneumonocytes have been identified around 23 to 26 weeks of gestation and they peak at 34 to 36 weeks.[49,50,53]

9.3.3 Chemical Composition of Surfactant

The discovery of surfactant revealed that it is composed mainly of lipid, particularly phospholipid and some proteins. Further studies identified it as lipoprotein with abundance in lecithin (saturated phosphotidyl choline) having a trace of cholesterol, and neutral lipids.

9.3.4 Mechanism of Action of Surfactants

The primary function of surfactant is to reduce the surface tension that lines the alveolus.[55,56,59] Surface tension is a force that is dependent upon the attraction of a molecule for an adjacent one. Consider a glass of water; under the surface, the water's molecules are attracted to each other with equal force from all directions because they are completely surrounded by other molecules. However, the situation is different for the surface layer of molecules because the forces of attraction are not equal from all directions. The air above the surface layer exerts little upward pull, and the balance of forces thus favor downward and horizontal directions. The force exerted by this imbalance of intermolecular attraction is surface tension.[49] Applying this concept of surface area contraction to the inner surface of spherical alveolar walls, surface tension tends to contract alveolar walls in the absence of an opposing influence, thus promoting alveolar collapse. In the normal lung, surface tension is reduced by surfactant. Without surfactant, surface tension forces increase directly with the collapse of alveoli during expiration, resulting in alveolar collapse.[49,52,54,60]

What is the mechanism involved in surfactant? Assume that a liquid contains two kinds of particles: surface-active and nonsurface-active molecules. Surface-active molecules, regardless where they are, tend to exert smaller attracting forces for other molecules. When concentrated at the surface, they dilute the molecules of the liquid and must, therefore, lower its surface tension. This is the role of surfactant. The low surface tension eliminates the muscular effort necessary to ventilate the lungs and keep them aerated, rendering stability to alveolar gas bubbles and keeping them from collapsing. By keeping alveoli open, atelectasis is prevented, lung compliance is improved and ventilation-perfusion is matched, thereby decreasing the work of breathing.[61,62]

Other functions of surfactant may include increasing the host-defense mechanism against pulmonary infections, and improvement in moderating the inflammatory response with the lung.

9.3.5 Indications for Surfactant Use

It has been shown that surfactant may appear as early as 24 weeks of gestation in the fetal lung. However, functional surfactant is generally present in the last 10% to 20% of the gestational period.[49] With the beginning of postnatal breathing, considerable force is exerted to overcome the high viscosity and inertia of the fluid that fills the air spaces at birth. The high pressures generated in the first few breaths are essential for lung expansion as well as moving fluid from the lung to establish air-fluid interface. As air enters the lung and the size of the airways narrows in the periphery, the surface tension in the air-fluid interface increases. The presence of adequate surfactant makes the clearance of fluid from the smaller airways more efficient; hence, less effort is needed to replace each unit of lung fluid with air.

Conversely, surfactant deficiency is clinically manifested in the premature neonate as RDS. On physical examination, the neonate has increased respiratory rate (tachypnea), retractions (labored breathing), grunting (prolonged end expiration), and is hypoxemic. X-rays show a diffuse reticulogranular pattern with air bronchogram and ground glass appearance. Lungs are poorly inflated, which can be related to the changes in surface properties in the air-liquid interfaces lining the alveoli. As mentioned earlier, in air spaces deficient in surfactant, there are increased surface forces requiring increased opening pressures which result in instability, loss of volume and consequently, lung collapse.[63-66] Due to increased oxygen requirement and increased work of breathing, metabolic function is compromised. In short, immature lungs require higher pressures to initiate alveolar fillings, and have little or no residual volume. The presence of adequate surfactant, on the other hand, decreases the pressure required to open the lungs, thus maintaining alveolar stability.[67-69]

9.3.6 Types of Commercial and Investigational Surfactants

There are several types of surfactant products available for clinical as well as investigational purposes. Some are modified natural surfactants, while others purely are synthetic. They contain diplomitoyl phosphotidyl choline (DPPC) with artificial spreading agent, or DPPC with human recombinant proteins.[66, 70, 71] In the United States, both Survanta (Ross Laboratories, Columbus, OH), and Exosurf (Burroughs Wellcome, Research Triangle, NC) are approved by the FDA for neonates. Survanta is derived from calf lungs, while Exosurf is completely synthetic and lacks protein. Curosurf (Chiese Farmaceutcio) is a European product made from pig lungs. Surfactant A-Tr (Akito-Tokyo) is a Japanese product, made from minced cow lung, used only in Japan.[62, 71]

9.3.7 Administration of Surfactant

Once the need for endogenous surfactant is indicated by the neonatologist, surfactant replacement therapy can be instituted as a prophylactic or preventive measure during which surfactant is instilled directly into the trachea of an intubated neonate. This can be performed either at the delivery room or the NICU.

In the United States, the dosage used is 100 mg surfactant/kg body weight, for either single, multiple or multiple-dose protocols.[66] There is some disagreement among clinicians in Europe and the United States as to the dosage and the frequency used. Ideal candidates are infants at risk for developing RDS, and infants with low birthweights which strongly suggest lung immaturity. Infants in whom the lecithin/sphingomyelin ratio is less than 2:1, as well as infants that are intubated and less than 48 hours old with increased oxygen requirement, may benefit from surfactant therapy.

9.3.8 Contraindications/Complications

Procedural complications resulting from the administration of surfactant include mechanical obstruction of the endotracheal tube, bradycardia due to hypoxia, and tube plugging. Reflux of surfactant may result from fast instillation as well as from a small endotracheal tube. Transient desaturation may occur which may necessitate increased oxygen requirement. There are reports that include pulmonary hemorrhage, retinopathy of prematurity, intraventricular hemorrhage as well as apnea associated with endogenous surfactant administration. Contraindications to endogenous surfactant administration may be the presence of anomalies that are incompatible with life such as terminal cardiac and congenital anomalies.

9.3.9 The Future of Surfactant

Exogenous surfactant therapy is now the standard of care in combating neonatal RDS.[72-74] It is clear from the ample data available that the benefit outweighs the risk. Some investigators are now determining if surfactant therapy could be a standard treatment in ARDS; there is some evidence that it can.[75]

Worldwide, the type of surfactant, doses, and mode of delivery will probably be modified as new surfactant drugs appear commercially. Aerosolized surfactant has already been tried on mammalian animals. Surfactant may be effective in infants with meconium aspiration, hypertension of the newborn and, possibly, in some other lung diseases.

The future may also bring the second or third generation of designer drugs of surfactant from recombinant DNA techniques.[66] It is imperative, however, to understand that surfactant therapy will not eliminate RDS, nor will it prevent bronchopulmonary dysplasia (BPD); rather, it decreases the incidence and severity of the disease but does not eliminate the clinical diagnosis. It will reduce the mortality and morbidity of neonates from RDS, as well as the prevalence of air leaks.[76]

The widespread use of surfactant will have a favorable result on the care of premature neonates with RDS and hopefully other groups of patients.[66,77] According to Dr. Alan Jobe, surfactants could also be used as vehicles in the distribution of antibiotics or other drugs in the treatment of a variety of lung diseases.[66]

9.4 Nitric Oxide

Nitric Oxide (NO), a gas under normal atmospheric conditions, is not to be confused with nitrous oxide (N_2O), also a gas used in the hospital environment. Although the mechanism of action of NO is only recently understood, the clinical application and use of NO is still in its infancy. Nitric oxide gas is not approved for widespread clinical use by the FDA. Current clinical applications are generally under NIH-approved research grants which follow strict protocols.

9.4.1 Physiology

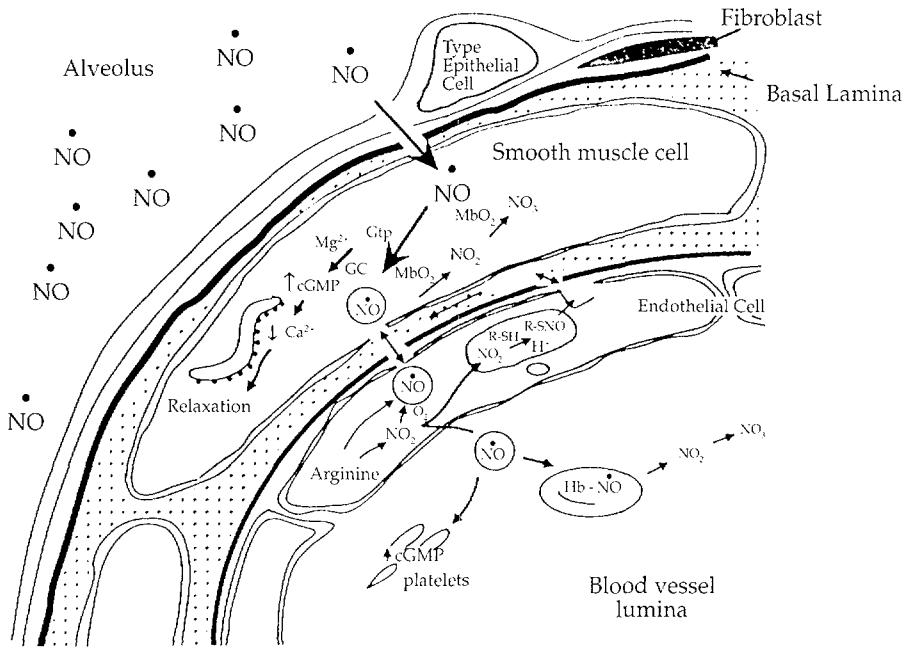
Nitric oxide is produced naturally by the human body in small amounts and acts on a large variety of organs and organ systems. For the purposes of this presentation, the discussion will be limited to the mechanisms of action of NO on the smooth muscles and pulmonary vasculature.

The inner lining of the blood vessels is composed of endothelial cells which produce a variety of chemicals. One of these chemicals is called endothelium-derived relaxing factor (EDRF). This substance appears to be NO itself or perhaps a similar NO-containing species such as nitrosothiol.[78] Furchgott has recently suggested that EDRF may be NO.[79] Palmer et al. has stated that EDRF and NO are identical.[80]

The EDRF/NO was first reported in vascular endothelium where it serves as a potent determinant of basal and induced vascular tone.[81] The vascular endothelium also produces potent vasoconstrictors.[82] Vascular tone can be thought of as a smooth muscle tug-of-war between constriction (reducing the vessel diameter) and relaxation (increasing the vessel diameter). The balance of these two forces is vascular tone. A schematic diagram of the present understanding of the mechanism of inhaled NO vasodilation is presented in Figure 9.2.

A wide variety of hormones and chemicals produced by the body will increase the calcium level in the endothelial cells. Calcium stimulates the production of EDRF/NO from L-arginine (an amino acid) by EDRF/NO synthase. Once produced, EDRF/NO diffuses to the vascular smooth muscle where another series of complex chemical reactions occur, which results in vasodilation. [EDRF/NO activates soluble guanylate cyclase (GC), resulting in the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP)]. EDRF/NO is recognized as a major vasodilator originating from the endothelium. The hypothesis that NO gas is a selective pulmonary vasodilator is based upon this premise.

Figure 9.2 — A schematic of the proposal routes of NO uptake and mechanism for pulmonary vasodilation. (from Fratacci M-D, Frostell CG, Chen T-Y, et al. Inhaled NO prevents heparin-protamine vasoconstriction. *Anesthesiology.* 1991;75(6):991.)



9.4.2 Properties of Nitric Oxide

Nitric oxide is a colorless, highly diffusible gas. It has a density of 1.04 (about the same as air). In combination with oxygen, NO forms a red-brown gas called nitrogen dioxide (NO_2), a highly reactive gas that is a toxic irritant to human lung tissue. When exposed to NO, NO_2 reacts readily to form dinitrogen trioxide (N_2O_3), which is soluble in water and forms either nitrous or nitric acid.

The reaction of NO with oxygen to form poisonous compounds is dependent on the concentration of oxygen and the square of the concentration of NO.[83] This means that the conversion of half of a 10 ppm concentration of NO to NO_2 would take about 7 hours in room air at 20°C. At a concentration of 100 ppm, the conversion would take about 40 minutes. High concentrations of oxygen will also affect the rate of conversion to NO_2. It is very important to limit the exposure time of NO to high concentrations of oxygen.

Because of its reactivity, NO is supplied in stainless steel cylinders of various sizes and in a variety of concentrations. It is noncorrosive; however, in the presence of oxygen and moisture, corrosive conditions will develop due to the formation of nitrous

and nitric acids. It is very important that the regulator, flowmeter, blender, ventilator, and any downstream fittings be constructed of stainless steel or corrosion-resistant materials.

9.4.3 Administration of Nitric Oxide

The administration of NO in the clinical setting is generally performed under an approved FDA or NIH grant and under strict research protocols. The industrial manufacturers of NO will not sell the cylinders of gas unless the clinician supplies the physician's investigational new drug (IND) number. This number is assigned by the FDA at the time the application to study the gas or drug was received.

There are several multicenter NO protocols in use around the country for the neonatal/newborn population. All have strict enrollment criteria. For example, to be enrolled, the neonate/newborn must be 34 or more weeks gestation, less than 7 days of age upon admission, mechanically ventilated on intermittent mandatory ventilation (IMV), in severe respiratory failure, displaying an arterial blood gas on 100% oxygen of less than 80 mmHg, and in persistent pulmonary hypertension (PPHN) without structural heart disease.[84]

Persistent pulmonary hypertension of the newborn, which used to be called persistent fetal circulation (PFC), is a serious consequence of pulmonary and cardiac difficulties. Infants with PPHN have increased pulmonary vascular resistance because deoxygenated blood is shunted across the patent foramen ovale and/or patent ductus arteriosus. Both structures allow blood to pass from the right side of the heart to the left in the fetus, but are supposed to close after birth. If these structures do not close, the result is pulmonary hypertension which produces systemic hypoxemia (low arterial blood oxygen levels). Persistent pulmonary hypertension of the newborn is also associated with hypertrophy and hyperplasia of the pulmonary artery smooth muscle.[85] Congenital heart lesions that increase pulmonary blood flow may also have pulmonary vascular smooth muscle abnormalities and pulmonary artery hypertension.

9.4.4 Regulations and Safety

Nitric oxide is considered by the Environmental Protection Agency to be an industrial pollutant. It is classified as a "Class A" poison gas by the Department of Transportation (DOT) and is shipped under a "Poison Gas" label. Occupational exposure is regulated by OSHA PEL and guided by NIOSH recommendations. As a result, time-weighted average exposure limits of less than 25 ppm with spikes to 100 ppm for less than 15 minutes have been established.[86] Remember that one puff from a cigarette will expose the smoker to 400 ppm to 1000 ppm of NO.[87]

Storage of NO is regulated under the 1991 Uniform Fire Code, Sections 80.301 and 80.303. It is recommended that NO be stored in an approved gas cabinet.

Requirements have also been developed by the microelectronics industry for the safe handling of toxic gases. Michael Boyle, Director of Cardiopulmonary Services at the University of Minnesota Hospital and Clinic, has developed standards in conjunction with the University of Minnesota Department of Environmental Health and Safety for the use of NO based on those of the microelectronics industry and the NIOSH Recommended Standards for Occupational Exposure to Oxides of Nitrogen. In a confidential pre-publication communication with the author, Mr. Boyle proposed

administrative as well as engineering controls.[88] Implementation of the following guidelines will assure a safe hospital environment when using NO.

Administrative controls include monitoring ambient concentrations of NO and NO_2, conducting pre-employment and annual medical examinations, posting areas where NO is used, informing and training affected employees, and evaluating work practices.

Engineering controls include administering NO in a room under negative pressure and exhausting completely to the outside, checking exhaust fans for leaks, storing NO in approved gas cabinets, scavenging equipment for discharged air, using type 316L stainless steel for piping, providing excess flow valves on each line, and assuring adequate check valves to prevent contamination by back flow or diffusion.

9.4.5 Monitoring Techniques

9.4.5.1 Chemiluminescence

Currently there are two types of NO analyzers on the market, both from the industrial sector. The first is the chemiluminescence type. It is represented by such manufacturers as Thermo Environmental Instruments Inc., Eco Physics, Dasibi Environmental Corp., and Thermo Electron Corp. The chemiluminescence analyzer is designed to measure and quantify the level of light emission of a given chemical reaction. Light generated by this chemical reaction has a specific wavelength which is usually expressed in nanometers, (nm, 10^{-9} meter) or in angstroms (10^{-10} meter). The level of intensity of the light is proportional to the level of the chemical reaction.

Since the early 1970s, it has been known that the reaction of NO with reactants like ozone (O_3) resulted in a light emission (hv). The direct measurement of NO by chemiluminescence is based on this reaction:

$$NO + O_3 \rightleftharpoons NO_2$$
$$NO_2 \rightleftharpoons NO_2 + hv$$

When NO in a gas sample reacts with excess O_3, some of the NO_2 generated is briefly in a higher excited state. It is very unstable and quickly reverts to the lower state. The change from the higher state to the lower state releases light (600 nm to 3000 nm with a peak at 1200 nm). It is represented by the following equation:

$$NO + O_3 \rightleftharpoons NO_2^* + O_3$$
$$NO + O_3 \rightleftharpoons NO_2 + O_2$$
$$NO_2^* \rightleftharpoons NO_2 + hv \text{ (about 600 nm to 3000 nm)}$$

To further complicate matters, not all NO_2 emits light. Some of it collides with other molecules, is deactivated, and produces no light. This deactivation by collision and reaction with other molecules is called quenching. Quenching is like throwing wet logs into an already burning fire or lighting a BBQ with half the charcoal wet with water.[89]

The typical chemiluminescence NO analyzer contains a vacuum pump (to aspirate the sample of gas to be analyzed), an O_3 generator (to produce O_3), a drying chamber (the gas sample must be free of humidity and particulates), a reaction chamber (has a temperature range of 300ºC to 7000ºC), a photomultiplier tube (PMT) — a light-sensitive cathode whose electrical output is proportional to the light intensity in the reaction chamber), filter, electronics, and an exhaust scrubber (so that the environment does not become contaminated with NO).

During the analysis, the aspirated gas sample is fed directly into the reaction chamber. Since NO_2 does not react with O_3, the light level detected by the PMT is due only to the amount of NO in the sample.

Part of the aspirated sample is routed to a converter to reduce NO_2 to NO. Since the routed sample already contains NO, the level of NO reaching the reaction chamber is the sum of the NO in the sample plus the amount reduced from NO_2. The NO level is then electrically recorded. The amount of NO_2 in the sample is determined by subtracting the first NO level from the routed, reduced NO sample reading (NO_X).

The considerations when using this type of analyzer are many. It is expensive — $9,000 to $17,000. It requires a long warm-up time and a considerable amount of expertise. A calibrating gas ($500 for 800 liters of 25 ppm NO) is required to verify the accuracy of the instrument. Since it was designed for the industrial market, an isolation transformer must be added if the analyzer is to be used in the patient care environment. It is also expensive to maintain.

9.4.5.2 Galvanic (Electrochemical) Analyzer

The second type of NO analyzer is the galvanic or electrochemical type. It is represented by the EIT Sensor Stik, the Pulmonox II, and the Bedfont Scientific NO and NO_2 monitors. The Sensor Stik for NO, for example, uses a membrane, sealed amperometric cell. It is maintenance-free, requires no filling, and exhibits a high degree of stability and repeatability. Repeatability and linearity errors are reported to be less than 2% of scale. The principle of operation is that NO undergoes an oxidation reaction which produces an electrical signal in proportion to the concentration of the gas being measured. The reaction at the sensing electrode is as follows:

$$NO + 2H_2O < -< NHO_3 + 3e^- + 3H^+$$

According to the manufacturer, the response time is not significantly affected by extremes in operating temperature (-40ºC to +50ºC) or pressure (0 psig to 10 psig). An adapter must be developed so that the EIT Sensor Stik can be used on the circuit of a ventilated patient. As with all sealed galvanic or electrochemical cells, the useful life is inversely proportional to the concentration of the gas being measured. The higher the concentration of the NO being measured, the shorter the life of the cell. Most manufacturers provide a 1 year warranty on the cell.

Another consideration is that a separate cell is required for the measurement of NO_2. If both NO and NO_2 are to be measured, then a specific cell must be purchased for each gas. The cells cost about $800 each, but as the use continues to increase, the price will probably decrease. The cells can also be purchased to detect a specific concentration range of NO or NO_2. As with the chemiluminescence analyzer, a calibrating gas is required to verify the accuracy of the cell.

9.4.6 Patient Safety

Smokers apparently can tolerate high levels of NO for short periods; however, the main risk associated with an overdose of NO appears to be methemoglobinemia.[90] More research is needed to determine the long term effects.

9.4.7 Future Directions with Nitric Oxide

Inhaled NO has been shown to be a rapid and potent bronchodilator.[91] As a result, NO may be considered as an alternative approach to treating various causes of bronchoconstriction such as asthma and bronchospasm. Because of the localized effects of NO, it could be administered to vasodilate specific lung regions and thereby improve ventilation-perfusion to those selected regions. It may also be used to improve the ventilation-perfusion to a single transplanted lung without affecting the other lung. Inhalation of NO in combination with the administration of NO-releasing drugs could provide a potent therapeutic approach to bronchodilator therapy.

There may also be a dark side to NO administration. Freeman has suggested that caution and more research is needed into the conditions wherein therapeutic doses of NO may also exert toxicity.[92]

9.5 *Liquid Ventilation*

A few years ago, the concept of liquid ventilation captured national attention with the release of the science fiction film "The Abyss." In a critical scene, the hero must disarm a bomb and uses a liquid ventilation system to enable him to get to the record ocean depth. The average movie-goer may consider liquid ventilation as fictional — it is not; nor is it a new concept.

For about 70 years, researchers have been using various fluids such as saline, silicones, and fluorocarbons to facilitate and support respiration. Winternitz and Smith used saline to treat victims of poisonous gas inhalation and discovered that lungs could tolerate large amounts of saline without subsequent damage.[93] However, saline is limited as a respiratory medium because of its high viscosity and density and its low oxygen solubility as compared to air. Kylstra et al. submerged mammals in hyperbarically oxygenated saline and found that they could survive and resume air breathing.[94] Subsequently, investigators using saline to explore the relationship between respiratory structure and function have produced a significant body of knowledge resulting in our current understanding of pulmonary physiology, bloodflow, ventilation, perfusion, and surfactant.

Numerous synthetic and natural oils, including silicone have been tried but are too viscous, nonvolatile, or too toxic. Investigators interested in liquid ventilation turned their attention to perfluorochemical fluid (PFC), a substance first produced during World War II as part of the Manhattan Project. A significant contribution to liquid ventilation was made by Clark and Gollan. In 1966, they were the first to use an oxygenated PFC to support the respiration of several small animals that were totally immersed in the breathing liquid.[95]

Another area of biochemical research, also by Gollan and Clark[96] as well as Kylstra,[97] was the application of liquid breathing to overcome the hazards of a hyper-

baric environment. They demonstrated that PFC-breathing mice could be rapidly decompressed without fatal decompression sickness. Apparently, the liquid-filled lung provides a barrier to prevent excessive inert gas from dissolving in the blood and tissues when exposed to large changes in the partial pressure.

9.5.1 Production and Properties of Perfluorocarbon Liquids

The electrochemical process for the production of fluorocarbons and derivatives was discovered by Professor J. H. Simons and has been developed on a commercial scale by 3M Company and recently by other manufacturers. The process involves the replacement of all hydrogens in the organic compound with fluorine by electrolyzing with anhydrous hydrofluoric acid. A review of the literature shows that a variety of derivatives have been used and include FC-43, FC-47, FC-72, FC-75, FC-77, FX-80, FC-80, FC-100, Caroxin-D, TWEEN 20, PAM, APF-140 (perfluorodecalin), PFOB (perfluorooctylbromide "Perflubron"), and Liquivent. The most recent product is a sterile perflubron called AFO 141 and is produced by Alliance Pharmaceuticals of San Diego, CA.

The physical properties of PFC liquids which make them suitable for medical applications include high oxygen and CO_2 solubility, low surface tension, high density, high viscosity, chemical inertness, insolubility in water, essentially nontoxic, and an absence of biotransformability. They also have a high temperature stability and require no unusual or special handling or ventilating techniques.

9.5.2 Applications

In the past, most of the research was performed with saline or PFC by either total immersion or by gravity-assisted ventilation from a reservoir to an intubated animal. Because these liquids are dense, viscous, and have different diffusion rates, respiratory work is required to breathe. Despite the high solubility of oxygen and CO_2 in perfluorocarbon liquids, increased work of breathing leads to inadequate ventilation and results in an accumulation of CO_2 and acidosis.

A significant contribution was made by Moskowitz[98] in 1970 and was later expanded by Moskowitz and Shaffer.[99, 100] They developed a demand-regulated liquid ventilator which allows the experimental animal to control the cycling of the ventilator that circulates the fluorocarbon liquid in and out of the lungs. The animal's own respiratory center establishes the tidal volume and rate while the mechanical ventilator reduces the respiratory work needed to circulate the PFC. The most important point is that effective delivery of oxygen and adequate removal of CO_2 in the liquid-filled lung is now possible.

Further studies by Modell[101] and Shaffer[102] have shown that experimental animals can breath PFC for extended periods without undesirable side effects and that a small amount of PFC is retained for up to 3 years. Two problems still exist with liquid ventilation. A small degree of metabolic acidosis remains which, according to Lowe et al.,[103] is related to hyperlactatemia secondary to a significant decrease in cardiac output and regional redistribution of blood flow. Lowe and Shaffer[104, 105] have also identified significant increases in pulmonary vascular resistance (PVR) and redistribution

of blood flow in the liquid-filled model. They suggest that the elevation of the PVR may be a contributing factor for the cardiovascular readjustments. These observations may limit the applicability of liquid ventilation to certain research efforts, and probably not neonatal ventilation.

9.5.3 Partial Liquid Ventilation

A new technique which has been shown to improve oxygenation and ventilation in experimental animals with severe lung injury is partial liquid ventilation (PLV). Because the use of PFC liquids on humans is limited, several multicenter study protocols have been funded to test the safety and efficacy of PLV with the perfluorochemical liquid AFO141 (a sterile, medical grade of perflubron) for the treatment of human newborns with severe infant respiratory distress syndrome (IRDS). Two protocols were recently approved by the FDA. One is for babies who do not respond to surfactant therapy, and the other is for babies who do not improve after at least 7 days on ECMO.[106] The studies have very specific criteria for admission. After admission, a PFC liquid functional residual capacity (FRC) dose of AFO141 of approximately 20 ± 10 ml/kg over a period of 10 to 30 minutes is administered intratracheally. A FRC dose is defined as that total volume of instilled AFO141 that provides a visible meniscus in the subject's endotracheal tube at the level of the superior chest wall on end-expiration within 1 to 3 seconds after disconnecting the subject from the ventilator. Supplemental doses of AFO141 are instilled as necessary to maintain a total lung volume of AFO141 approximately equal to the FRC. The rate of supplemental replacement of AFO141 (due primarily to evaporation) is expected to be approximately 2.0 ml/kg/hr.

Unlike liquid ventilation where the PFC liquid is circulated in and out of the lungs, PLV only fills the FRC and does not require a specially modified mechanical ventilator. (For a discussion of FRC and other lung volumes, please refer to *Respiration*, pages 11-13, in this series). Once the terminal alveoli are filled with liquid, collapse from the high surface tension is prevented. For example, an adult may have a surface tension of about 2 dynes/cm, but a distressed infant may have a level of 63 dynes/cm. Liquid ventilation and PLV eliminate the air/liquid interface, recruit the regions of the lung with atelectasis, distend the lung parenchyma, improve lung compliance and eliminate high surface tension. The result is an effective distribution of gas exchange and pulmonary stability. The reduction of surface tension also allows the clinician to use lower inflation pressures during mechanical ventilation and avoid the damaging effects of barotrauma. Following a brief period of liquid ventilation, a neonate would then make the transition to gas ventilation.

9.5.4 Other Considerations

Perfluorocarbon liquids have a higher heat capacity when compared to gas, which allows the lung and pulmonary circulation to act as an internal heat exchanger. Properly heated PFC would help stabilize the internal temperature of a distressed infant. Since the temperature regulation by a premature infant is not well developed, PFC could reduce the energy expended and thereby reduce stress.

Perfluorocarbons could also help distribute pharmaceuticals to the lung and pulmonary vasculature in a rapidly acting manner. The surface area of the lung available in this manner is enormous.

Additional research is needed into the cardiopulmonary effects of PFC and its observed metabolic acidosis effect. Further research probably will result in refinements in PFC liquids to address density, surface tension, and heat transfer concerns.

More research and experience with human infants ventilated with PFC liquid will determine the continued use of AFO141 and similar products.

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10.0 ENVIRONMENTAL NEONATOLOGY

The neonatal environment and the effect it has on infants has recently become a major topic of research investigation; the term environmental neonatology is now in the literature.[1] Neonatal developmental concerns, posed by researchers such as Heidelese, Als and others, have become key factors in evaluating the neonatal intensive care unit (NICU) environment.[2]

Premature infants have underdeveloped central nervous systems which are easily overstimulated leading to infant stress.[3] It is now thought that emphasizing a quiet, calm, low-light, low-stress environment for the neonate will provide a better outcome for the infant and their concerned family. Studies by Als indicate a decrease in complications associated with hospitalization when the neonate has individualized care based on behavioral assessment.[5]

This section will address the role of NICU environmental factors, such as noise and ambient lighting, on the neonate.

10.1 Early Years in the NICU

The practice of sequestering extremely ill newborns into NICUs first occurred approximately 30 years ago. To care for these infants, a pediatrics subspecialty — neonatology — came into existence in the mid 1970s.[1] At that time, the neonatologist was a specialist whose primary role was the management of mechanical ventilators, pharmacology, and technology specific to the care of the neonate. The professional NICU caregiving staff included nurses, respiratory therapists, and ancillary staff specialized in the care of these lower birthweight infants.

In the beginning, NICUs were environmentally small and cramped, and even though neonatal mortality was high, the number of infants being sent to the NICUs increased. During the 1960s, ill full-term infants were preferentially sent to the NICU rather than the pediatric floor.[1] Due to an increasing survival rate, many NICU environments became seriously overcrowded by the early 1980s.

To combat overcrowding most units were remodeled. In the remodeling process, planners attempted to correct a perceived space problem by designing larger, open NICUs designed to house many infants in one large room. Adjoining smaller isolation rooms were built for those infants with suspected or proven communicable diseases. The design emphasis, however, was placed on staff efficiency, not consideration of the infant's environment.

The potential for a noise-filled environment was increased because the majority of staff worked in one room. Routine talking, common caregiving noises, and the sound of hand washing reverberating in stainless steel sinks created a very noisy NICU.

The NICU environment in the early years was not only noisy, it was also bright. Twenty-four hour per day lighting was important because each infant was under nearly constant observation. Because reliable oximetry technology was still a few years in the future, any cyanotic change in skin color, warning of the low oxygen state known as hypoxia, would have had to have been detected by one of the caregivers.

Neonatal units are typically remodeled every 10 to 15 years due to changes in technology and the needs of the hospital to remain within code requirements.[6,7] As many NICUs approach their next major remodel, new developments and research is causing designers to rethink the NICU environment.[8,9]

10.2 Current NICU Technology

The technological revolution of the past several years has changed many of the rules for designing and remodeling neonatal environments.[7,10] Reliable monitoring for neonatal heart rate, respiratory rate, blood pressure, and oxygen saturation is now available. Oximeters which work well in low-light situations are commonplace; it is now possible to dim the lights when caregiving tasks are not being performed because neonatal hypoxia will be detected by the oximeter. Alarms can be configured and set by the caregiver to sound audibly when the infant falls below or rises above preset oxygen saturation values.

10.3 An Environment for Neonates, Caregivers, and Family

When the topic of the NICU environment is discussed, we must differentiate whose environment we are taking about. Is it the environment of the neonate, or is it the environment of the professional caregiving staff? Or, is it the environment of the neonate's family? All of these environments must be considered as they are all important in the successful care of the neonatal patient.

Family-centered neonatal care is becoming very important in the NICU environment.[11] For many years the right of privacy for the neonate and the neonate's extended family had to be ignored. The rights of the physicians, nurses, and others to have instant access to the neonate often obviated the family's rights. Compared to the adult patient in the same hospital, the neonate had few rights.

A change in attitude about the rights of the neonate and family is in progress — this is known as family-centered neonatal care.[12] Family-centered neonatal care, which is one method for increasing the participation of the neonate's family in the care of the infant,[13] changes the environment perceived by the infant's family.

The basic tenets of family-centered neonatal care are:

- Family-centered neonatal care should be based on open and honest communication between parents and professionals on medical and ethical issues.
- To work with professionals in making informed medical treatment choices, parents must have available to them the same facts and interpretation of those facts as the professionals, including medical information presented in meaningful formats, information about uncertainties surrounding treatments, information from parents whose children have been in similar situations, and access to the chart and rounds discussions.
- In medical situations involving very high mortality and morbidity, great suffering, and/or significant medical controversy, fully informed parents should have the right to make decisions regarding aggressive treatment for their infants.
- Expectant parents should be offered information about adverse pregnancy outcomes and be given the opportunity to state in advance their treatment preferences if their baby is born extremely premature and/or critically ill.

- Parents and professionals must work together to acknowledge and alleviate the pain of infants in intensive care.
- Parents and professionals must work together to ensure an appropriate environment in the NICU.
- Parents and professionals should work together to ensure the safety and efficacy of neonatal treatments.
- Parents and professionals should work together to develop nursery policies and programs that promote parenting skills and encourage maximum involvement of families with their hospitalized infant.
- Parents and professionals must work together to promote meaningful long-term follow-up for all high-risk NICU survivors.
- Parents and professionals must acknowledge that critically ill newborns can be harmed by overtreatment as well as undertreatment, and we must insist that our laws and treatment policies be based on compassion. We must work together to decrease disability through universal prenatal care.[13]

10.4 Birth — The Changing Environment

The birth process represents one of the most dramatic environmental changes — the infant leaves the warm, fluid, dark, sound-muffled environment of the mother and is suddenly thrust into a bright, loud, and, above all, cold environment. Some degree of heat loss is responsible for the biochemical cascade of events which accompanies the change from being a fetus to becoming an air breather; however, too much heat loss can be very detrimental to the newborn.[14]

The radiant warming table is the first environment a neonate experiences after being born. Warm blankets are replaced under the infant until all excess amniotic fluid is absorbed. If needed, the environmental air is oxygen-enriched. This table allows for the initial examination, observation, and care of a newborn. It provides supplemental heat replacement for any heat loss from convection, conduction, radiation, or evaporation.

10.5 The Neonate's Internal Environment

Once stabilized in the extrauterine environment, the neonate is transported to the NICU. Once again the infant is placed on a warming table or, in some units, into an isolette. This is when high-tech monitors are applied to the neonate, and immediate feedback from the neonate's internal environment is available to caregivers.[15] Heart rate, respiratory rate, blood pressure, oxygen saturation, and many other vital signs are available.

The neonate communicates the effectiveness of care through their internal environment via the monitors — too little oxygen and the oximetry value falls; too much oxygen and the oximeter value reaches 100%. If the neonate has too little drive to breathe, the respiratory rate will display a flat line and soon the heart rate and blood pressure will fall. The patient monitor and professional clinical assessment skills are very important during this initial phase.

10.6 The Neonate's Immediate Environment

In the care of the ill newborn, the environment immediately around the infant must be altered many times. For example, servo-controlled temperature sensors adjust the temperature of the air around the infant to keep the thermal-supported environment close to normal body temperature.

If a neonate needs an oxygen-enriched environment, they're placed into an oxygen hood. This allows caregivers to closely monitor the exact percentage of oxygen enrichment, as well as temperature and humidity. If the oxygen percentage continues to rise, the physician may elect to provide an artificial airway and mechanically ventilate the infant with either high-frequency, patient-synchronized or conventional mechanical ventilation. Both oxygen hoods and mechanical ventilators warm and humidify the cold, dry medical gas, which decreases neonatal heat loss.

10.7 The Professional Caregiver Environment

The NICU environment must also address the needs of caregivers.[16] It must be a place where the staff can effectively and efficiently perform a very stress-filled job. Coping with physical environment problems while dealing with life-and-death situations can contribute to staff burnout.[17]

In the NICU, the height of equipment and electrical connections, as well as accessibility to pumps, ventilators, and emergency supplies must be optimized for convenience.[17] Medical documentation, whether handwritten or entered on a computer keyboard, takes the eyes and attention of the caregiver away from the patient. This increases caregiver stress and underlines the need for monitoring tools that keep the caregiver's attention with the patient.

10.8 Environmental Lighting

Clinicians concerned about providing developmentally appropriate care for preterm infants have identified the bright lights of the NICU as a source of excess stimulation that causes disturbances in infant state and sleep patterns.[4,18] Lighting extremes in the NICU can lead to biochemical and physiological changes in the retina that increase the risk of long-term deficits in visual acuity and color vision.[19] The brightness of ambient environmental light has been linked to the incidence of oxygen-induced retinopathy of prematurity, especially in infants weighing less than 1000 gms at birth.[20] Light may make the eyes more sensitive to the damaging effects of oxygen on immature vessels by altering the retinal vasculature or the cell metabolism.[20] Studies by Ackerman et al.[21] and Keith et al.[22] have published a negative finding on this hypothesis.

The foot-candle, a measurement of illuminance, is the incident light striking a surface at a given point. In the past, general lighting levels of NICUs were 60 foot-candles to 100 foot-candles, which allowed evaluation of the infant's skin color at any place in the unit.[23] As a comparison, illumination levels recommended by OHSA for offices is 40 foot-candles to 50 foot-candles.[24] The Illuminating Engineering Society (IES) recommends that the maximum brightness for an NICU patient looking up at the ceiling should be 90 foot-candles.[25] Glass observed that the incidence of retinopathy of prematurity in two infant intensive care nurseries was greater among infants exposed to high illumination (60 foot-candles) than among infants kept under reduced lighting (25 foot-candles).[20] Newly designed or remodeled NICUs should be able to provide ambient lighting at levels recommended by the IES of 10 foot-candles to 20 foot-candles.[26] Ideally, the ambient lighting for the premature patient should be adjustable between 1 foot-candle and 60 foot-candles.[23]

The use of multiple switching or fluorescence dimming systems can aid in the diurnal light-dark cycle in the NICU environment. Diurnal rhythms are characteristic features of human behavior, and it has been suggested that such rhythmicity may be essential for normal growth and development.[27] Continuous light exposure disrupts the normal regenerative process in the retina and alters retinal metabolism. The photoreceptor cells are constantly in a cyclic state, breaking down and building up. The normal process of breakdown and renewal is linked to the dark-light-dark cycles.[29] The cycled day-night NICU environmental patterns may have a protective retinal effect on premature eyes.[20,28]

Medical or surgical procedure lights that provide no more than 150 foot-candles to 200 foot-candles of illumination to the bed should be available to each infant.[23] The American Academy of Pediatrics/American College of Obstetrics and Gynecologists states that 60 foot-candles is sufficient for most procedures. The Task Force Guidelines from the Society for Critical Care Medicine recommends 100 foot-candles to 150 foot-candles for procedures. The IES recommends from 50 foot-candles to 1000 foot-candles for medical examinations.[30] Some phototherapy lamps have been measured at 1000 foot-candles.[21] The heating lamps used to warm infants have been measured at 200 foot-candles to 300 foot-candles; phototherapy lights at 300 foot-candles to 400 foot-candles.[20] These levels may represent a danger to the developing retina. When used, procedural lighting should be directed away from the eyes of the infant, or the infant's eyes should be covered.[31]

Although windows are important for the establishment of day and night cycles, it is important to protect the infant's eyes from the glare of direct sunlight.[29] Peak light exposure for the infant has been associated with supplemental lighting sources such as phototherapy lights, procedure lights, and, most dramatically, extensive direct window exposure which supplements artificial lighting at levels up to 1000 foot-candles.[24]

In many NICUs, light exposure is typically 24-hour per day throughout an infant's hospital stay. Because hospital stay is a function of the degree of immaturity and medical complications, light exposure is usually greatest for the lowest birth weight infants, who are the most vulnerable to vision problems.[32]

10.9 Environmental Infection Control Issues

Neonates, especially those born preterm and low birthweight, are very prone to infections. All staff, parents, and visitors must observe a prescribed length scrub before touching neonates. One of the most common methods of passing pathogens from one infant to another is by inadequate handwashing.[33] Therefore, the clinicians who care for these infants must observe strict handwashing practice between patients. The goal is to keep the NICU environment as infection-free as possible. A hospital-acquired nosocomial infection is a medical complication that may add to length of stay.

All equipment used on infants must be cleaned according to established policies and procedures. The cleanliness of the isolettes, warming tables, life-support ventilator, and breathing circuits must be maintained. All medical procedures involving patient contact require gloves and a cover gown. All used needles and sharps should have a separate waste receptacle to prevent environmental contamination or injury. Scrub sinks, paper towel dispensers and appropriate waste receptacles are an integral part of the NICU environment.

To maintain environmental air quality, the temperature must be kept between 72°F and 78°F with relative humidity between 30% and 60%. A minimum of six air exchanges per hour is recommended with a minimum of two exchanges being filtered outside air.[34]

10.10 Environmental Noise

Since 1974, the Environmental Protection Agency has recommended that the average 24-hour sound pressure level to prevent annoyance in a hospital be 45 decibels (dB) as measured on the A-weighted scale (dBA). (The A-weighted scale is used because it most closely resembles the frequency response of the human ear). Although no standards specific to the neonate are available, in 1970, OSHA set standards for the adult worker at 80 dBA as the highest sound level that does not produce damage. Ninety dBA is the limit imposed in industry as the highest safe level for an 8-hour period for adults, 95 dBA for 4 hours, 100 dBA for 2 hours, and 115 dBA for 15 minutes.[38] The 1983 Occupational Safety and Health Act Amendment identifies adult working exposure to 85 dBA as an action level where exposed workers must be part of a hearing conservation program. This admendment requires that workers at an exposure level of 90 dBA use ear protection and be included in the hearing conservation program.[40] It is important to note that sound pressure level approximately doubles with every 3 dBA increase.[39]

The American Academy of Pediatrics guidelines for perinatal care suggests that noise levels be kept less than 75 dBA at all times.[41] Researchers over the past 3 decades have measured sound levels in the NICU at 50 dBA to 90 dBA with sound pressure level peaks as high as 120 decibels.[35,42,43] As a measure for comparison, the sound of the spoken voice is 70 dBA and the sound of light machinery is 90 dBA.[44] Long et al. found that many NICU noises greater than 70 dBA were attributable to staff conversation, laughter, and activities such as opening and closing metal trash can lids and isolette porthole drawers.[35] Gadeke demonstrated that sound levels of 70 dBA to 75 dBA disturbed the sleep of one-half to two-thirds of infants and children after 3 minutes.[45]

Noise can also be caused by the high pitch whistle of supplement oxygen delivered directly into the incubator of through an oxygen hood.[46] A defective bearing on an incubator fan motor can also produce loud and potentially damaging noise.

The American Academy of Pediatrics recommends that the noise level inside isolettes be kept below 58 dBA.[36] Youngblut et al. suggests that the infant experiences whole-body vibration while lying inside incubators. Incubators only muffle sound when the motor is off; when an infant is inside, the incubator's fan provides continuous, pervasive white noise at 51 dBA.[43] Neonates often live in this environment of continuous noise for weeks and, sometimes, months.

The incidence of sensorineural hearing impairment is 4% in low birthweight infants, and 13% in very low birth-weight infants — both considerably higher than the 2% incidence among all newborns. The risk is even higher if the infant is exposed to ototoxic drugs.[43] Loud noise in the animal model has been shown to cause permanent hearing impairment through damage to the inner ear and to the auditory nerves. Sound levels which are prolonged and intense can directly damage the exquisitely fine stereocilia of the cochlea directly and permanently.[43]

Noise pollution in the NICU environment is avoidable. Whereas lighting may be a technological problem, noise abatement can result by simply educating the staff about the detrimental effect noise pollution has on neonates. For example, studies indicate that many of the sound level spikes recorded in NICUs are associated with staff laughter and caregiving tasks.[35] Of concern is the finding that loud environmental sounds are often associated with periods of oxygen desaturation of infants.[36]

The sound level spikes generated by NICU equipment having built-in alarms generally startles or awakens infants. The manufacturers of equipment used in the NICU should be encouraged to provide alarms which can be adjusted to acceptable sound pressure levels.

One method of diminishing sound levels in the NICU environment is to group neonates in smaller pod rooms of four to six infants per pod. The current area recommendation is 100 ft^2 per infant bedspace,[23] a spacing that also assists in infection control issues such as physical spread of disease.

10.11 The Environment and Neonatal Development

Als has suggested that there is a constant and continuous organism-environment interaction in the environment in which a neonate matures.[48] If this is so, then the environment plays an important role in the infant's development. Als et al. and Schultz suggest that individualized nursing care based on behavioral assessments of critically ill neonates can improve outcomes.[2,49]

The most critically ill or immature neonates require aggressive care and frequent interventions that necessitate handling and manipulation.[50] These infants have poorly developed organ systems that must continue to develop, mature, and adapt to the artificial, highly technical, and stressful environment of the NICU.[49,50] Vandenberg has identified environmental light, sound levels, and caregiver events as stressors that contribute to making the NICU an abnormal environment for the neonate.[52] Negative physiologic responses to handling may include a rise in both intracranial pressure and blood pressure, a rise in monitored carbon dioxide levels, and a fall in monitored oxygen levels.[36] Noise produces hypoxemia in preterm infants and the arousal it trig-

gers affects oxygenation, blood pressure, and cerebral blood flow — all of which can lead to intraventricular hemorrhage, a possible antecedent of developmental disability.[4,36,43]

Hypoxia is associated with damage to all major organ systems of the body. In effect, it causes a power failure within the cell. Hypoxia interferes with the oxidative metabolism and the generation of adenosine triphosphate, which is the special carrier for cellular energy.[53] Hypoxemia, inadequate blood oxygenation, is defined as a blood oxygen tension less than 50 mmHg.[53,54] It causes critical damage to the central nervous system and may result in a decreased quality of life for the infant. The effects of hypoxemia are particularly alarming in view of the increased risk and incidence of intraventricular hemorrhage in preterm infants.[43] Any caregiving event which results in a spike or fall in the blood pressure may rupture fragile brain capillaries. Moderate size hemorrhages may result in cerebral palsy. Large hemorrhages in the brain may lead to hydrocephalus and/or developmental disability.[55]

Minimal handling policies and appropriate signs on incubators or warming tables of infants at risk may reduce the incidence of multiple hypoxemic episodes. Setting aside specific rest periods so that others do not disturb infants who display wide physiological changes may help prevent intraventricular hemorrhage.[55]

10.12 Tempering the Neonatal Environment

In utero, the fetus is in deep sleep approximately 80% of the time with very few interruptions.[56] One study reports that in the NICU, an infant's sleep is disturbed an average of 132 times in 24 hours with undisturbed rest periods ranging between 4.6 minutes to 9.2 minutes.[57] Lawton suggests that infants in the NICU spend only approximately 20 minutes in deep sleep each day and, therefore, are essentially sleep deprived.[58] Noise, glare, and sleep deprivation associated with intensive care units are acknowledged to be major stressors for both adults and children.[59] The process of structuring a physical and social environment supportive of the individual infant's immature or dysmature nervous system becomes an integral component of care in the hospital setting, as well as in home and community.[5] Studies by Als et al. have documented the disruptive effects of an NICU on infants — sleep state is disturbed, excessive noise and light are stressful, and the patient expends calories on startle and stress reactions instead of growth.[2]

In the mid 1980s, Als designed a study which divided infants less than 1251 gms and less than 32 weeks gestational age into two groups.[2] One group received standard NICU care. The other group was nurtured in a tempered NICU environment with caregivers trained to assess the behavioral cues as delineated by Als.[61] Sleep and quiet time periods were observed. Care procedures were clustered to encourage minimal handling. Als and Lawton et al. published the results of this study in 1986.[2] Using the developmental approach, neonates in the experimental group weaned significantly faster from the mechanical ventilator, had fewer days on supplemental oxygen, and fewer gavage feeding days. Neurodevelopmental follow-up resulted in higher scores for the experimental group than the standard NICU care control group.[2]

In a replication study published in 1994, Als and Lawton et al. found that the experimental developmental group showed significant reduction in hospital length of stay, reduction of age at discharge, improved weight gain at 2 weeks after due date, reduced incidence of intraventricular hemorrhage, and decreased severity of chronic

lung disease. All these factors contributed to the fact that this group had a reduced hospital cost.[3] These studies and others, which are ongoing, provide potent information for the discussion about the effects of the NICU environment on the neonatal patient.[4]

10.13 Security of the NICU Environment

The NICU area is generally staffed by highly specialized individuals who all know each other. A stranger in the area is immediately observed, and must be accompanied by a parent to even gain access inside the NICU. Most NICUs have a front door which is staffed with an individual who greets the parents and others. Doors which are not physically monitored can be video-scanned by security, and outer doors to common hallways can be locked. Security has become a complex and multifaceted issue in hospitals and the NICU is no exception. In protecting the neonate, both external sources as well as familial sources must be considered. All hospital nurseries should have procedures for dealing with the threat or reality of kidnapping or abduction. As to be expected, healthy babies are more desirable to those who are motivated to acquire infants in this most nefarious way.

A more common threat to the neonate is unintentional harm from a well-meaning parent. Parents may want to help in the care of their child by answering alarms or adjusting IV pumps. While this behavior is more likely in pediatric or longer term settings, parents must be made aware of the complex and critical nature of their child's care. It is important that the NICU be a safe and secure environment for all those who enter.

10.14 References

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11.0 GLOSSARY

Accelerated ventricular rhythm — The rhythm of the beats of the ventricles of the heart that are faster than the normal rhythms; occurs when an ectopic focus in the ventricles fires at a rate of 50 to 100 bpm.

Adult respiratory distress syndrome — A form of restrictive lung disease due to abnormal permeability of either the pulmonary capillaries or the alveolar epithelium.

Alveoli — The tiny air sacs at the end of the airways in the lung; composed of very thin flat cells that form the network for gas exchange between fresh air and venous blood.

Apnea — A transient stoppage of breathing.

Arrhythmia — Any irregularity in the force of the heartbeat.

Arteries — Vessels or tube-like structures through which the blood passes away from the heart to varies parts of the body.

Atrial arrhythmia — The irregular rhythm of contraction or firing of the atrium of the heart.

Atrial fibrillation — The extremely rapid and disorganized pattern of the depolarization of the atria.

Artial flutter — The extremely rapid depolarization of the atria at rates of 250 to 350 bpm.

Atrioventricular node (AV node) — A mass of specialized cells in the right atrium, medial to the right atrioventricular valve and continuous with the other atrial cells and with the atrioventricular bundle; often divided by electrophysiologists into three functional regions: the atrio-nodal (AN), the nodal (N), and the nodal-His (NH).

Base impedance — The base value of impedance used for both children and adult electrocardiogram electrodes; usually around 500 Ohms.

Baseline wander — A drifting in the recording of a signal; random and slow deviations from the reference line of a signal recorded with respect to time.

Bradycardia — An abnormal heart rate of 60 or fewer bpm.

Bronchus — Bronchi, plural; any of the larger air passages of the lungs having an outer fibrous coat with irregularly placed plates of hyaline cartilage, an interlacing of smooth muscle, and a mucous membrane of columnar epithelial cells.

Capacitance — The proportionality constant relating the electric charge of a device that stores electric energy to the voltage across the two conductive elements of the device.

Cardiac arrhythmia — An alteration of either time or force of the rhythm of the heartbeat.

Cardiac diastole — The dilation or period of dilation of a chamber of the heart.

Cardiac systole — The contraction or period of contraction of the heart or one of its chambers.

Central apnea — Absence or suppression of the signal stimulating the inspiratory muscles of respiration.

Clark Electrode — An oxygen measuring sensor developed in 1956. Named after the sensorís designer Leland C. Clark J., M.D.

Compliance — A measure of how easily the lung distends when a gas passes through; the reciprocal of elasticity.

Conduction — The transfer of energy from the molecules of a body to the molecules of a solid object in contact with that body.

Convention — The transfer of thermal energy from the molecules of the body to the molecules of an adjacent gas.

Damping ratio — A percent of critical damping. Structures with critical damping return to their static or neutral position in the shortest time without oscillation.

Deadspace gas — The amount of gas left in the conducting airways at the end of the breath or gas that reaches capillaries with no blood supply.

Detector — Device for determining the presence of something.

Diaphragm — A primary muscle in the abdomen that elongates the thoracic cavity during inspiration and is innovated by the right and left phrenic nerves from the spinal cord.

Diastolic pressure — The point of least pressure in the arterial vascular system. The failure of the diastolic pressure to drop in proportion to the systolic pressure is a danger sign.

Doppler effect — The apparent frequency of waves, such as sound, varies with change in distance between the source and the receiver. The frequency seems to increase as the distance decreases and to decrease as the distance is increased.

Doppler principal — An apparent change in the frequency of waves, as of sound or light, occurring when the source and observer are in motion relative to one another, with the frequency increasing when the source and observer approach one another and decreasing when they move apart.

Dyshemoglobins — Faulty, incorrect, malformed hemoglobin.

Elasticity — A measure of the force with which the lung fibers attempt to recoil after deflation; the reciprocal of compliance.

Electrocardiogram (ECG or EKG) — The signal traced by an electrocardiograph; used to diagnose heart disease that modifies the electrical activity of the heart.

Electrocardiography — The set of procedures that measure the electrical activity of the heart and record it on an electrocardiogram.

Electrode — An electric conductor through which a current enters or leaves a substance in contact with this device.

Electrode contact noise — Noise produced by the contact of an electrode with the skin.

Environmental neonatology — The environmental factors in a NICU.

Evaporation — The total heat transfer by energy-carrying water molecules from the skin and respiratory tract to the drier environment.

Extracorporeal membrane oxygenation — Prolonged extracorporeal cardiopulmonary bypass via extrathoracic cannulation in patients with acute, reversible cardiac or pulmonary failure refractory to conventional medical or pharmacological management.

Fetal hemoglobin — Is composed of two alpha and two gamma chains while adult hemoglobin is composed of two alpha and two beta chains.

Forced expiratory volume (FEV) — The amount of air forced out of the lung.

Functional residual capacity (FRC) — The amount of gas in the lung when the lung elastic forces and the thoracic forces are equal but pulling in opposite directions.

Functional saturation (%SaO2) — The sum of the oxygen saturation of the four hemoglobin species in the blood.

Hemoglobin — The iron-containing protein in red blood cells that carries oxygen.

High-frequency ventilation — Includes any mode of ventilation that supports gas exchange using small tidal volumes and high ventilation rates.

Hyaline membrane disease — See Respiratory distress syndrome.

Hyperbilirubinemia — Excessive amount of bilirubine in the blood.

Hypopnea — Abnormally slow and shallow breathing.

Hypoxemia — Deficiency of oxygen in the blood; also hypoxia.

Infrared radiation — For practical purposes any radiant energy within the wavelength range 770 to 106 nm is considered infrared energy.

Impedance — A measure of total opposition to current in a circuit or air through an airway.

Inspiration — The intake of air into the lungs; occurs when alveolar pressure falls below the atmospheric pressure; a form of negative breathing.

Inspiratory cycle — The inspiratory component of the ventilatory cycle under the control of the inspiratory neurons at the end of the nerves from the medulla of the brainstem.

Inspiratory reserve volume (IRV) — The maximum amount of air that can be inhaled following a normal quiet inspiration.

Intermittent positive pressure breathing (IPPB) — Also called mechanical ventilation; the situation in which the alveolar pressure causes the capillary to collapse.

Intraarterial catheter — A tubular medical device for inserting into an artery to permit injection or withdrawal of fluids, to keep passages open, or to measure internal pressure.

Intrapleural pressure — The pressure surrounding the lung.

Left-to-right shunting — In reference to the patent ductus arteriosus, describes the direction of blood flow from the aorta to the pulmonary artery.

Korotkoff sounds — Noises created by the spurting blood from the compressed brachial artery which produce turbulence and vibrations within the vessel.

Mean arterial pressure (MAP) — The mean blood pressure in the arteries.

Mechanical ventilation — Aiding or supporting a patientís ventilation using a device to inspire air into the lungs and to extract air from the lungs; use during anesthetic surgery and in intensive care units.

Metabolic rate — The rate of utilization of energy.

Motion artifact — The mechanical modulation of the path length of the transmitted light due to motion as measured by a pulse oximeter sensor.

Natural Frequency — The frequency at which a body vibrates due to its own physical characteristics when the body is distorted and then released, while restrained or supported at specific points.

Newborn — Born recently. Term applied to human infants less than a month old.

Obstructive apnea — Respiratory effort without maintaining an open airway.

Oscillometric method — The principle that as an occluding cuff deflates from a level above systolic pressure, the artery walls begin to vibrate or oscillate as the blood flows; these vibrations will be sensed in the transducer system monitoring cuff pressure.

Oxyhemoglobin — The combination of oxygen with hemoglobin in an easily reversible reaction.

Partial pressure of oxygen (POI) — The pressure that oxygen would exert if it were alone in a container.

Partial pressure of arterial oxygen (PaO2) — The partial pressure of oxygen in arterial blood.

Partial pressure of carbon dioxide (PaCO2) — The partial pressure of carbon dioxide in arterial blood.

Patent ductus arteriosus (PAD) — The abnormal persistence of an open lumen in a fetal blood vessel connecting the aorta to the pulmonary artery. The direction of blood flow through the PAD is dependent on the pressure gradient between the aorta and pulmonary artery.

Periodic breathing — In infants, the three or more central apneas of at least 3 and or more than 15 seconds long with each separated by no more than 20 seconds of stable regular breathing.

Photoplethysmography — A system of measurement that differentiates arterial from venous blood using light reflectance or light transmission through vascular tissue to measure arterial pressure waveforms generated by the cardiac cycle.

Premature beat — A cardiac contraction occurring before the normal one.

Premature ventricular contractions (PVCs) — Signals seen on electrocardiograms that indicate the premature contractions of the ventricle of the heart.

Pulse oximeter — Instruments that measure patient ventilation using a pulse waveform continuous monitoring system.

Pulse oximetry — A noninvasive method to measure the color of the hemoglobin molecule, and therefore oxygen saturation of the arterial blood, through the skin.

Pulse pressure — The difference between the systolic and diastolic pressure.

Radiation — The net rate of heat loss in the form of electromagnetic waves between the body and the environmental surfaces not in contact with the body.

Resistance — Opposition or counter-acting force; an impediment to air flow through the tissue.

Respiration - The process of exchanging waste carbon dioxide or oxygen in the body; at the cellular level, the release and use of energy to accomplish cellar processes.

Respiratory distress syndrome — Delivery of an infant who has not matured to the point where the lungs can manufacture the lecithin-rich pulmonary surfactant. This results in collapse of the alveoli with consequent cyanosis and hypoxia.

Right-to-left shunting — In reference to a patent ductus arteriosus, is the direction of blood flow from the pulmonary artery to the aorta.

Sensor — A device that responds to a physical stimulus (such as heat and light) and transmits a resulting signal.

Servo control — Applies to any servo mechanism in which a loop input signal generated by a transmitting transducer can be compared to a loop feedback signal generated by a compatible or identical receiving transducer to produce a loop error signal.

Severinghaus Electrode — A carbon dioxide measuring sensor developed in 1958. Named after the sensorís designer John W. Severinghaus, M.D.

Signal processing — A system having circuit elements associated with its radiatory elements that perform functions such as multiplication, storage, correlation, and time modulation of the input signals.

Sinoatrial node — A microscopic collection of atypical cardiac muscle fibers at the superior end of the sulcus terminalis and at the junction of the superior vena cava and right atrium; also called sinus node. The cardiac rhythm normally begins at the sinoatrial node so that this node is also known as the pacemaker of the heart.

Spectrophotometry — The measurement of transmittance and reflectance of surfaces and media as a function of wavelength.

Stratum corneum — The outer layer of the epidermis, consisting of cells that are dead, keratinized and desquamating.

Sudden infant death syndrome (SIDS) — The interruption of breathing in an infant that leads to death; also called ìcrib deathî; usually occurs within the first year of life.

Surfactant — An agent that lowers surface tension.

Superventricular tachycardia — Cardiac rhythms that are incessant at 160 bpm to 200 bpm with the presence of P waves and an 1:1 relationship to the QRS complex.

Systemic circulation — The blood flow from the left ventricle through the aorta and all its branches (arteries) to the capillaries of the tissues and its return to the heart through veins and the venae cavae, which empty into the right artium.

Systolic pressure — Maximum blood pressure. This occurs during contraction of the ventricle.

Tachyarrhythmias — Irregularity of heart beat combined with rapid rate.

Temperature coefficient — The ratio between the rate of change in resistance with temperature to the resistance of the thermistor at a given temperature.

Transcutaneous gas monitoring — The measure of oxygen and carbon dioxide partial pressure on the skin surface using a gas-measuring electrode.

Transducer — A device that converts fluid pressures to electrical voltages. Standardized transducers are interchangeable because they generate the same amount of voltage output per unit of fluid pressure applied. The resting output voltage of the transducer is known as the offset with the atmospheric pressure applied to the sensing membrane, which is often some other value than 0 volts.

Transmittance sensors — A photoreceiver that functions to measure the transmission of light through a monitoring site.

Transthoracic impedance — A respiratory effort transducer that measures the impedance between two ECG electrodes by passing a constant high frequency, low ampere current in a modified Einthoven Lead I or Lead II position.

Thermistor — An electron device that makes use of the change of resistivity of semiconductor with the change in temperature.

Thermocouple — A pair of dissimilar conductors so joined at two points that an electromotive force is developed by the thermoelectric effects when the junctions are at different temperatures.

Valsalva maneuver — Attempt to forcibly exhale with the glottis, nose, and mouth closed. If the eustachian tubes are not obstructed, the pressure on the tympanic membranes will be increased. Maneuver can also be done with just the glottis closed, but only intrathoracic pressure will be increased. This causes increased intrathoracic pressure, slowing of the pulse, decreased return of blood to the heart, and increased venous pressure.

Valsalva sinuses — Three dialations in wall of the aorta behind the flaps of the three aortic semilunar valves.

Ventilation — The movement of air in and out of the chest; includes the movement or changes in both the thoracic cage and the lung.

Ventilation perfusion ratio — The ratio that determines the amounts of oxygen and carbon dioxide exchanged in each unit.

Ventilatory cycle — The complete cycle of inspiration and expiration of gases controlled by the medulla of the brainstem; regulated primarily by negative feedback mechanisms.

Wheatstone bridge — An instrument or circuit consisting of four resistors in series with a galvanometer linking the junction between one pair and the other; used to determine the value of an unknown resistance when the three other resistances are known.

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Spacelabs Medical, Inc.
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ISBN 1-882588-50-9
P/N 061-0471-00, Rev. A